VOLUME 63 NUMBER 2

ARCHIVES OF NEUROLOGY AND PSYCHIATRY

FEBRUARY 1950

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $12.00

Entered as Second Class Matter Jan. 7, 1918, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

CONTENTS OF PREVIOUS NUMBERS

JANUARY 1950. NUMBER 1

Archives of Neurology and Psychiatry

VOLUME 63 FEBRUARY 1950 NUMBER 2

RELATION OF MIGRAINE TO CEREBRAL ANEURYSM

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THE RELATION of migraine and other forms of periodic headache to intracranial aneurysm and subarachnoid hemorrhage has been commented on with considerable frequency. The association of migraine and intracranial aneurysm has been mentioned by Fearnsides,[1] Critchley and Ferguson,[2] Jefferson,[3] Richardson and Hyland,[4] Dunning,[5] Rowbotham,[6] Dandy,[7] Wolff,[8] Sugar and Tinsley[9] and Alpers and Schlezinger.[10] Goldflam[11] and Adie[12] were concerned with the relation of migraine to subarachnoid hemorrhage rather than to intracranial aneurysm per se.

The series of verified cases of intracranial aneurysm at the Jefferson Hospital contains 3 cases in which recurrent periodic headache was present for many years before an aneurysm was suspected. Two of these cases fulfil the criteria for migraine; the other case of recurrent periodic headache had some, but not all, of the features of migraine. Instances of ophthalmoplegic migraine have not been included in this study.

From the Department of Neurology, Jefferson Medical College of Philadelphia.

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9. Sugar, O., and Tinsley, M.: Aneurysm of the Terminal Portion of the Anterior Cerebral Artery, Arch. Neurol. & Psychiat. **60**:81 (July) 1948.

10. Alpers, B. J., and Schlezinger, N. S.: Aneurysms of the Posterior Communicating Artery, Arch. Ophth., to be published.

11. Goldflam, S.: Contributions on Etiology and Symptomatology of Subarachnoid Blood, Deutsche Ztschr. f. Nervenh. **78**:158, 1923.

12. Adie, W. J.: Permanent Hemianopia in Migraine and Subarachnoid Hemorrhage, Lancet **2**:237, 1930.

In this communication, I propose to discuss the relation of headache to intracranial aneurysm and to indicate that a presumptive diagnosis of intracranial aneurysm can be made clinically before the appearance of the usual signs of rupture.

REPORT OF CASES

CASE 1.—M. R., a white woman aged 58, was admitted to the neurologic service of the Jefferson Hospital on Sept. 21, 1947. Her history revealed that she had had headaches on the right side in childhood associated with flashes of light in the right eye and nausea. After several years, the headaches decreased in intensity and frequency but otherwise were unchanged. They tended to recur at two to four week intervals and lasted twenty-four to forty-eight hours, disappearing spontaneously. She obtained some relief from staying in a dark room. In June 1947 the patient had a "nervous breakdown." On July 9, 1947, about two months before admission, while on sick leave, she experienced a very severe headache on the right side, which was aggravated by talking or moving her head; quiet rest in bed reduced the intensity of the headache, which persisted until a week later. At that time, during an argument, she felt "something burst" in her head. Within twenty-four hours she noted drooping of the right eyelid and double vision on looking up or down, but not on looking to either side. Shortly thereafter the headache became localized in and around the right eye and was accompanied with nausea and vomiting. It was aggravated by moving her head and by coughing, sneezing and straining, and was relieved only by narcotics. This headache persisted unabated until she entered the hospital.

She had had a thumping sound in both ears synchronous with her pulse, and episodes of vertigo for several years.

The physical status was normal.

Neurologic examination revealed profound prostration; increased light striping of the retinal vessels; a slightly larger right pupil, which reacted sluggishly to light and consensually; ptosis of the right eyelid; loss of upward and downward movement of the right eyeball and impairment of inward movement, and generally overactive deep reflexes. There was no evidence of meningeal irritation.

The urine gave a 3 plus reaction for albumin and contained many pus cells and occasional red blood cells. The blood count showed 3,940,000 red cells, 71 per cent hemoglobin and 8,200 white cells, of which 58 per cent were neutrophilis and 42 per cent lymphocytes. The Wassermann and Kahn reactions of the blood were negative. Lumbar puncture revealed an initial pressure of 150 mm. of water, 3 cells per cubic millimeter, 25 mg. of total protein per hundred cubic centimeters, a negative Wassermann reaction and a normal colloidal gold curve. The roentgenogram of the skull revealed nothing abnormal. The electrocardiogram failed to reveal clearcut evidence of myocardial disease.

While the patient was under observation, she was found to have a labile blood pressure; the systolic pressure varied from 114 to 180 mm. of mercury, and the diastolic pressure, from 64 to 128 mm.

Four days after admission the patient suddenly complained of increased pain in her head, had a generalized convulsion and died twenty-five minutes later.

Postmortem examination showed arteriosclerotic changes throughout the aorta, but most prominent in the abdominal aorta, and moderate congestion of the liver. There were ruptured aneurysm of the right posterior communicating artery and an unruptured small aneurysm of the right middle cerebral artery.

Comment.—This woman had had typical migraine headaches, which were always on the right side, associated with nausea and vomiting, since childhood. Ten weeks before admission, she was again seized with a headache on the right side, but this differed from her usual sick headaches in that it was severer and more persistent. A week later, while under emotional stress, she felt something burst inside her head, and within twenty-four hours there appeared ptosis of the right eyelid and diplopia and the headache became localized in and around the right eye. Severe headache and ocular signs persisted until she was admitted to the hospital in a moribund state. Postmortem examination revealed systemic atherosclerosis and two aneurysms of the circle of Willis. The larger aneurysm probably ruptured when she had the bursting sensation in her head.

Case 2.—E. B., a white woman aged 58, was admitted to the neurologic service of the Jefferson Hospital on Oct. 20, 1948, with a history of headaches in the right frontal area, associated with nausea and vomiting but without visual symptoms, since she was 8 years old. They persisted intermittently until the menarche, at the age of 15, when they became frontal in location, occurred monthly in relation to her menstrual periods, persisted for twenty-four hours and were associated with nausea and vomiting. They were occasionally relieved by bromoseltzer® [13] or acetylsalicylic acid. Six weeks prior to her admission, while the patient was watching a baseball game, she was suddenly stricken with severe pain above and behind the right eye, involving the right side of the nose and the right maxillary region. The pain was severe and constant for twenty-four hours and then became dull with daily exacerbations lasting several hours. The headaches were not associated with nausea or vomiting. Three weeks after onset of the headache there was noted drooping of her right eyelid, followed in ten days by sudden, excruciating pain in the right side of the face. The next morning, the pain was less severe, but the right eyelid became completely closed and could not be voluntarily raised. Diplopia was noted when the right eyelid was passively elevated. The headaches and ocular symptoms persisted until the patient's admission to the hospital.

The past medical history revealed that the patient had had two miscarriages; there was also one neonatal death following a cesarian section performed because of severe toxemia of pregnancy. Cataracts were removed from both eyes in 1944. Her family history revealed that her mother, maternal grandmother and a maternal aunt had had migraine.

Physical examination disclosed a grade 2 systolic murmur in all valvular areas and slight enlargement of the heart.

Neurologic examination revealed bilateral aphakia, a dilated, completely inactive right pupil, ptsosis of the right eyelid, loss of all movements of the right eyeball except outward ones and pronounced retinal arteriosclerosis. There were no signs of meningeal irritation.

While she was in the hospital, the systolic blood pressure ranged from 130 to 180 mm. and the diastolic pressure from 70 to 106 mm. of mercury.

The urine was normal. The blood count showed 3,950,000 red cells, 71 per cent hemoglobin and 4,200 white cells, with 63 per cent neutrophils, 33 per cent

13. Each dose contains 2.5 to 3.5 grains (0.23 to 0.16 Gm.) of acetanilid and 5 to 7 grains (0.33 to 0.45 Gm.) of sodium bromide.

lymphocytes and 4 per cent monocytes. The Wassermann and Kahn reactions of the blood were negative. Lumbar puncture was not performed. Roentgenologic examinations of the skull and chest revealed a normal condition. Roentgenologic studies of the soft tissues showed calcification of the arteries of the arms, legs and abdominal aorta.

An arteriogram of the right internal carotid artery, performed five days after her admission, revealed a saccular aneurysm at the junction of the internal carotid and the posterior communicating arteries.

Since severe pain persisted in the head and face, Dr. J. Rudolph Jaeger performed a craniotomy in the right frontotemporal region, even though the patient was considered a poor surgical risk. The right internal carotid artery was found to be sclerotic and dilated to three to four times its normal size. At a point about ½ inch (1.3 cm.) after the internal carotid artery entered the skull, a broad-based aneurysm, 2 cm. in length and 1 cm. in diameter, compressed the right third nerve. The base of the aneurysm was closed with an aluminum clip.

After her operation the right-sided headache disappeared, but the patient had dull aching pains over both eyes, a feeling of pressure over the vertex and throbbing in both temples; these pains responded well to acetylsalicylic acid.

Comment.—This patient, who had a strong family history of migraine, had typical right-sided migraine headaches before the menarche. The headaches then began to involve both frontal regions, occurred monthly and were associated with nausea and vomiting. The nature of her headaches changed at the onset of the present illness, differing from those previously experienced in that they were severer and of longer duration and were located around the right eye and on the right side of the face. Three weeks later there were noted partial ptosis of the right eyelid and diplopia. After three more weeks, in the course of a severe headache, there appeared complete ptosis of the right eyelid and diplopia. The patient also had a labile blood pressure, with a tendency to hypertension. She had severe retinal arteriosclerosis, roentgenographic evidence of sclerotic changes in the vessels of the extremities, sclerosis of the right internal carotid artery on exploration and an aneurysm of the right internal carotid artery. Although headache was present after operation, it was unlike that previously experienced.

Case 3.—G. O., a white girl aged 19, was admitted to the neurologic service of the Jefferson Hospital on Feb. 20, 1946, with the complaint of intermittent headaches since she was 7 years old. Initially, the headaches were in the frontal region and over the vertex, and they tended to recur once a month; but in June 1945, about seven months before the patient's entrance into the hospital, they began to occur at weekly intervals. They were relieved by acetylsalicylic acid. On Jan. 4, 1946, in the course of a severe head cold, headache over the vertex and pain in both eyes became apparent, and during the subsequent week the patient began to experience blurred vision. At the end of that week she was unable to raise the right eyelid, and on passively raising it she saw double; she noted that she was unable to rotate her right eye medially. Although the ocular symptoms persisted, there was gradual improvement in her headache until six days before her admission (February 14), when, on sharply turning her head to the left, she began

to have persistent, intense pain on the top of her head. She had had four or five bouts of nausea and vomiting since January 1946. This was associated with anorexia and loss of about 15 pounds (6.8 Kg.) in weight.

General physical examination revealed nothing significant.

Neurologic examination revealed complete ptosis of the right eyelid; absence of movements of the right eyeball except for outward rotation; dilatation of the right pupil with complete inactivity to light and consensually; sluggish response of the left pupil to light, but prompt response in accommodation and consensually; blurring of the nasal margins of both optic disks and fulness of the retinal veins, and slight unsteadiness of gait. She faltered in the heel to toe test, but she stood well on either leg alone.

The urine was normal. The blood count showed 3,450,000 red cells, 61 per cent hemoglobin and 8,000 white cells, of which 60 per cent were neutrophils and 40 per cent lymphocytes. The Wassermann and Kahn reactions of the blood were negative. Lumbar puncture showed an initial pressure of 250 mm. of water; the spinal fluid contained 7 cells per cubic millimeter and 26 mg. of total protein per hundred cubic centimeters and gave a negative Wassermann reaction. A roentgenographic examination of the skull, including the optic foramens, revealed nothing abnormal.

An arteriogram, performed on March 1, 1946, revealed no abnormality. Air encephalograms made ten days later revealed a normal ventricular system, but there was constant failure of the chiasmic cistern to fill.

In view of the lack of filling of the chiasmic cistern, together with the ocular findings, an exploratory craniotomy in the right frontal area was performed (March 22) by Dr. J. Rudolph Jaeger; a fusiform aneurysm, about 1 cm. in diameter, of the internal carotid artery was found.

Comment.—A 19 year old girl had had periodic monthly headaches, involving the frontal region and vertex, since she was 7 years old. Initially they were not associated with nausea, vomiting or ocular symptoms. Seven months prior to admission, they changed in frequency, appearing at weekly intervals. Six weeks prior to her admission, in the course of a head cold, the character of the headache again changed, becoming constant, severe and confined to the vertex, and in a short time she noted ptosis of the right eyelid and diplopia. Because of the persistence of her symptoms, exploration was performed, despite a normal arteriogram, and an aneurysm of the internal carotid artery was found.

COMMENT

In reviewing the cases of recurrent headache in this series, it became apparent that a history of three distinct types of headache may be obtained in cases in which an aneurysm is later found. Initially there is episodic headache, of years' duration. This is followed by a change in the type of the headache one to several months before the patient seeks hospitalization, the change being increased severity, frequency or duration of the headache, alone or in combination, and at times associated with a change in its location. Finally, there appears the severest and most persistent headache, often accompanied with paralyses of extraocular muscles.

In cases 1 and 2 the headaches fulfil the criteria for migraine as enunciated by Riley [14] and Wolff.[8] The headaches started in childhood in both instances; in case 2 there was a strong family history of sick headaches. The headaches were episodic, related to the menses and usually unilateral. In case 1 the headaches were always on the right side; in case 2 they were on the right side when they first appeared, but they became frontal in location at the menarche. There were associated gastrointestinal symptoms in both cases; in case 1 there were associated ocular symptoms in the form of flashes of light. The headaches in case 3 also started in childhood and were episodic. They were located in the frontal region and over the vertex, but there is no recorded evidence of visual or gastrointestinal disturbances at the onset. The headache in this instance, however, conformed to the cerebral type of migraine of Critchley and Ferguson.[2]

In all these cases the nature of the headache changed one to seven months before the patient's admission to the hospital. In case 1 a very severe headache occurred on the right side ten weeks before admission; this headache persisted for a week, when the patient noted a "bursting sensation" in her head. In case 2, six weeks before admission, the patient suddenly began to experience severe pain in the region of the right eye and the right side of the face; this pain persisted for twenty-four hours and was followed by constant dull pain, with daily exacerbations, in the same location, the ache continuing for the next five weeks, until her admission to the hospital. In case 3, the headache was altered in frequency only, the interval between attacks changing from monthly to weekly seven months before she entered the hospital.

A third type of headache occurred in all the cases. This was the severest type of headache, which in the first 2 cases came on abruptly and was associated with ocular signs. In case 1, within twenty-four hours after the patient felt something burst in her head, pain appeared in and about the right eye, associated with drooping of the right eyelid and double vision. In case 2, partial drooping of the right eyelid, which occurred three weeks after the onset of the second type of headache, was followed ten days later by severe excruciating pain in and around the right eye and the right side of the face; this was followed in twelve to twenty-four hours by complete ptosis of the right eyelid and by diplopia. In case 3 there was intense pain over the vertex associated with blurring of vision and with ptosis and diplopia about six weeks before the patient came into the hospital; her headache gradually improved, to return with increased severity five weeks later. In all of these cases the last type of headache was continuously present until the patient entered the hospital.

14. Riley, H. A.: Migraine, Bull. Neurol. Inst. New York **2**:429, 1932.

Of primary importance is the question whether the migrainous headache beginning in childhood is the initial symptom of an aneurysm which is already present and is of sufficient size to cause symptoms, whether the migraine and the aneurysm are merely related phenomena or whether the migraine is functional but plays a part in the formation of the aneurysm. There is considerable diversity of opinion concerning this question. Dandy,[7] in reviewing 108 cases of aneurysm, found 1 instance of migraine and 1 of periodic unilateral headache. He stated unequivocally that the aneurysm must have been the cause of the migrainous attacks of many years' duration and that the migraine was probably due to involvement of the sympathetic nerve fibers in the arterial wall. Both Buerki[15] and Rowbotham[6] classified a symptomatic form of migraine which may be attributed to intracerebral aneurysm, and Fearnsides[1] noted that it is not uncommon for episodic headache to be the first clinical manifestation of an aneurysm. Magee[16] stated that migraine in young persons for whom no relevant family history is obtained should arouse the suspicion of an aneurysm. Critchley and Ferguson[2] noted that typical migraine attacks occur too frequently in patients who have died later of intracranial aneurysm to be considered a coincidence. Goldflam[11] and Adie[12] also found typical migraine headaches in patients who have later had a subarachnoid hemorrhage.

On the other hand, Jefferson[3] stated that it was possible, but not probable, that the migraine headache of twenty years' standing in a patient with an aneurysm of the internal carotid artery had the aneurysm as its basis. Richardson and Hyland,[4] who obtained a history of migraine in 4 cases of a series of 118 cases of spontaneous subarachnoid hemorrhage and 8 cases of large ruptured aneurysm, stated that in a fatal case in which autopsy was performed no definite association between the headaches and the aneurysm could be detected, either clinically or pathologically. Wolff,[8] on the other hand, reported that of 46 patients with subarachnoid hemorrhage, 7 had migraine and 12 had periodic recurrent headache, both unilateral and bilateral. He stated the opinion that migraine headache in patients who later have a subarachnoid hemorrhage and aneurysm is probably independent of the presence or absence of aneurysm; the patient may have both structural and functional anomalies of the cranial circulatory system.

Critchley and Ferguson[2] stated the opinion that repeated migrainous attacks may affect the structure of a cerebral blood vessel so as to facilitate a terminal vascular accident. Wolff[8] expressed the belief that such a situation was a distinct possibility, the repeated migraine

15. Buerki, C.: Studies on Ophthalmoplegic Migraine, Confinia neurol. **4**:54. 1941.

16. Magee, C. G.: Spontaneous Subarachnoid Hemorrhage, Lancet **2**:497, 1943.

headaches contributing to the formation of an aneurysmal sac in the congenitally weak portions of the cerebral arteries. According to Dunning,[5] it is possible that distention or constriction of cranial arteries occurring during attacks of migraine precipitates rupture or occlusion at the site of an aneurysm or arteriosclerotic narrowing, the migraine disorder being only a contributing cause.

Most of our patients in whom intracranial aneurysms were later found had no symptoms prior to dilatation of the vessel wall sufficient to cause neighborhood signs, or before rupture of the aneurysm. In the cases in which migraine was present, the migraine headaches could well have been due to functional alterations in the cranial and cerebral vascular supply and initially unrelated to the presence or absence of an aneurysm. However, migraine headache, when present, could contribute either to formation of aneurysm in a weak portion of the arterial wall or to dilatation of a minute aneurysm which was already present. Among the factors contributing to the formation of aneurysm during an attack of migraine, Wolff [8] noted high intravascular pressure, stretch of relaxed cerebral vessels with each cardiac systole and, possibly, edema of the arterial walls. Forbus [17] demonstrated congenitally weak portions of arterial walls due to defects in the media, especially at the points of bifurcation of the vessels. The presence of a minute aneurysm of the basilar artery in early infancy was reported by Forster and Alpers,[18] who described an aneurysm 1 mm. in diameter which involved the basilar artery of a 13 week old child. While it is unlikely that the mere presence of a weak portion in the vascular wall or a minute aneurysm is the cause of migraine in patients predisposed to this disorder, it is conceivable that the vascular factors present during a migraine headache, in a patient so predisposed, may result in the formation of an aneurysm or the dilatation of a minute aneurysm which is already present. It is also noteworthy that arteriosclerotic changes were present in both the middle-aged women who had had migraine headaches, apparently without permanent ill effects, for about fifty years. The physiologic changes present in the branches of the circle of Willis during a migraine headache could have resulted in permanent aneurysmal dilatation when the additional factors of a labile blood pressure and arteriosclerosis were superimposed on the functional changes.

Adie [12] pointed out the relation of consistently unilateral headache to aneurysm, stating that headache which shifts from side to side is

17. Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47**:259, 1930.

18. Forster, F. M., and Alpers, B. J.: Aneurysm of the Circle of Willis Associated with Congenital Polycystic Disease of the Kidneys, Arch. Neurol. & Psychiat. **50**:669 (Dec.) 1943.

evidence against aneurysm. On the other hand, consistently unilateral migraine would tend to suggest the possibility of an aneurysm on the same side as the migraine. Dandy [7] and Wolff [8] also mentioned this relation. In cases 1 and 2, the headache when unilateral was always on the right side, i. e., the side on which an aneurysm was later found. Wolff [8] pointed out a case in which an aneurysm was observed on the right side of the circle of Willis in a patient who throughout her life had attacks of migraine just as often on the right side as on the left. A similar case was reported by Schmidt [19]; in this case a large aneurysm was observed in the right middle cranial fossa in a patient whose previous headaches had occurred chiefly on the right side, but were also experienced on the left side. Whether consistently unilateral migrainous headaches in cases in which an aneurysm is later found is more than fortuitous is open to question. If the headaches were due to intermittent episodic aneurysmal dilatation, it is likely that there would be accompanying paralyses of extraocular muscles. In addition, it is questionable whether an aneurysm which has dilated, and thus caused a specific type of headache, would be able to return to a symptomless condition in the course of a few hours.

In all our cases there was a change in the nature of the headache, before the appearance of neurologic signs, which could point to an intracranial complication, such as aneurysmal dilatation or rupture. During a period ranging from one to several months before the patients entered the hospital, there was noted an increase in the severity, frequency or duration of the headache and, in the second case, a change in the location of the pain as well. In case 1 the headaches became severe and constant, and in case 2 they were constant but dull, with daily exacerbations. In both cases these headaches persisted until neurologic signs developed. In these cases it is quite likely that aneurysmal dilatation had occurred and that it was of sufficient magnitude to cause continued pain from the pain-sensitive arteries of the circle of Willis, in these cases the posterior communicating and internal carotid arteries. Wolff [8] remarked that some patients who have had the usual features of periodic unilateral headaches for years may from time to time experience a somewhat different type of headache, which is bilateral or generalized, intense and long lasting. Although he did not attribute these headaches specifically to an aneurysm, he stated that this headache may involve not only the dilated arteries of the dura and those outside the cranium but the cerebral arteries as well.

The likelihood of an intracranial complication being present in the third case when the headaches changed in character, becoming more frequent, is not quite so apparent. Certainly, in this case the change in the headaches should have aroused the suspicion that whatever process was present had become aggravated.

19. Schmidt, M.: Intracranial Aneurysms, Brain **53**:489, 1930.

This point in the chronology of the patient's illness is of practical importance and is in agreement with Bailey's [20] observation in commenting on the possibility that an intracranial tumor may develop in a patient with migraine. He stated that in a patient with migraine any change in the phenomena of the attacks or an undue increase in frequency or severity should put the physician on the alert. If the patient is subjected to diagnostic procedures before further dilatation or rupture of an aneurysm occurs, the outlook is better. Arteriographic studies at this time may well reveal the presence of an aneurysm which has previously not been suspected.

When the character of the headache changes for the third time, becoming severer and associated with paralyses of extraocular muscles, the patient is obliged to enter the hospital. By this time, it is obvious that a severe intracranial disturbance is present, but the patient is not in nearly so good a physical condition as before. In the first case, it is probable, in view of the observation of ruptured aneurysm at autopsy, that a subarachnoid hemorrhage occurred at the time the patient noted a bursting sensation in her head. The rupture must have occurred some time previous to her entry into the hospital, since there was no blood in the specimen of spinal fluid examined several days before she died. In the other cases, the pain and neurologic signs can be attributed to the dilatation of the aneurysm alone, since there was no evidence of rupture of the aneurysm at operation.

CONCLUSIONS

1. Three cases of recurrent headache in which intracranial aneurysm was later verified at operation or autopsy are reported.

2. In all these cases the nature of the headache, which had been present for periods of from twelve to fifty years, changed from one to several months before the patient entered the hospital. This change should arouse suspicion of the development of an intracranial complication, to be interpreted as permanent dilatation of a congenitally weak portion of the arterial wall or dilatation of a minute aneurysm. It is suggested that the patient be closely observed and possibly subjected to diagnostic procedures at this time.

There is a further change in the character of the headache at the time of massive dilatation and/or rupture of the aneurysm which is already present. This change is usually accompanied with neighborhood signs in the form of palsies of the extraocular muscles, and the diagnosis of the intracranial aneurysm is made more readily.

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20. Bailey, P.: Intracranial Tumors, ed. 2., Springfield, Ill., Charles C Thomas, Publisher, 1948.

THE PHENOMENA OF SENSORY SUPPRESSION

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IN THE study of sensation it is seldom emphasized that there is a continuous stream of sensory impulses to the thalami and cortices, and that any new stimulation is merely a phasic activity of this continuous process.[1] If this stream of impulses from the exteroceptive and interoceptive systems were reported to the consciousness, one would be constantly occupied in evaluating these barrages of messages, and constructive activity would be very difficult. A mechanism must exist to regulate these incoming impulses, to permit only the important and the urgent to reach the consciousness, especially when the attention is focused elsewhere. It is here proposed that this mechanism is supplied by the sensory suppressor systems originating in the sensory strip areas of the cortex. It is likewise proposed that the phenomenon of "sensory extinction" to bilateral simultaneous stimulation is a manifestation of such physiologic suppression.

The existence of distinct projections from the visual, auditory and somatic cortices to the sensory nuclei of the thalami has long been known.[2] Head and Holmes [3] suggested that these pathways supplied an inhibitory influence on the thalami, the absence of which resulted in excessive reaction to stimuli.[3] Foerster [4] supported this view. Brouwer [5] stated the belief that the corticothalamic projections modify the sensitivity of the primary receptive centers, to render them more susceptible to incoming impulses—a mechanism of sensory attention.

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1. Adrian, E. E.: General Principles of Nervous Activity, Brain **70**:1 (March) 1947.

2. Cited by Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1943, p. 264.

3. Head, H., and Holmes, G.: Sensory Disturbances from Cerebral Lesions, Brain **34**:102 (Nov.) 1911.

4. Cited by Fulton,[2] p. 268.

5. Brouwer, B.: Centrifugal Influence on Centripetal Systems in the Brain, J. Nerv. & Mental Dis. **77**:621 (June) 1933.

That this cortical regulation of the thalamus would have to be bilateral was soon evident from the accumulation of studies indicating that some sensations were bilaterally represented in the thalamus and cortex. Auditory sensation is so extensively represented bilaterally that a unilateral lesion of the medial geniculate body, or Heschl's gyrus, causes only slight loss of hearing, and this bilaterally.[6] The exteroceptive sensations of light touch, superficial pain and temperature transmitted in the spinothalamic tracts are not entirely crossed.[7] This fact is especially evident in chordotomy for intractable pain, in which unilateral chordotomy is a failure and bilateral chordotomy a success.[7] Stimulation of the thalamus or cortex unilaterally with strychnine has produced hypersensitivity on both sides of the body.[8] Foerster [9] stimulated the cortex in man and the patient experienced bilateral paresthesias. In another study Gellhorn [10] found that stimulation of one sciatic nerve resulted in cortical discharges in the sensorimotor areas of both sides.

The role of the sensory suppressor strips in the regulation of motor activity has been well established through the work of Hines, Dusser de Barenne, McCulloch and Garol. In 1941 it was also observed that stimulation of any one of the suppressor strips, 4s, 8s, 2s, or 19s, suppressed the electrical activity of the entire hemisphere, the sensory areas as well as the motor areas.[11] Suppression of the sensory cortex was further investigated by Barker and Gellhorn.[12] They found that stimulation of the suppressor strips diminished the effect of both somatic and visceral afferent impulses in the cortical projection areas. Unilateral stimulation of the suppressor strips was reflected in both the ipsilateral and the contralateral cortex. The role of these suppressor strips was emphasized by the finding that unilateral stimulation of the peripheral nerves resulted in excitation of the suppressor areas of both cortices.[10]

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6. Spiegel, E. A., and Sommer, I.: Neurology of the Eye, Ear, Nose and Throat, New York, Grune & Stratton, Inc., 1944, p. 21.

7. Cited by Fulton,[2] p. 265.

8. Dusser de Barenne, J. G.: Central Levels of Sensory Integration, A. Research Nerv. & Ment. Dis., Proc. **15**:274, 1935. Dusser de Barenne, J. G., and Sager, O.: Sensory Functions of the Optic Thalamus of the Monkey (Macacus Rhesus), Arch. Neurol. & Psychiat. **38**:913 (Nov.) 1937.

9. Foerster, O., cited by Dusser de Barenne.[8]

10. Gellhorn, E.: Effect of Afferent Impulses on Cortical Suppressor Areas. J. Neurophysiol. **10**:125 (March) 1947.

11. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: Functional Organization of Sensory and Adjacent Cortex of the Monkey, J. Neurophysiol. **4**:324 (June) 1941.

12. Barker, S. H., and Gellhorn, E.: Influence of Suppressor Areas on Afferent Impulses, J. Neurophysiol. **10**:133 (March) 1947.

It is proposed that these findings of generalized cortical suppression accompanying a volley of sensory impulses is a fundamental mechanism of sensory perception. It is common experience that there is a great tendency of one circuit of impulses to dominate the consciousness, that seldom can man do more than one thing at one time with any appreciable accuracy. For example, distracting visual stimuli at a lecture may result in enough suppression of auditory impulses that several sentences of the lecturer may be "missed." Likewise, during intensive reading other sensations may be so suppressed that even a loud call to dinner or hunger contractions may not register until the stream of visual concentration is broken. If the competing stimuli are of sufficient intensity, no amount of suppression is adequate, and several stimuli are reported to the consciousness, with resulting inefficiency of perception. A common example of this is the difficulty in reading in a very noisy room, or in concentrating on visual or auditory stimuli while severe head pain or visceral pain is being reported to the consciousness.

Since sensory impulses are continuously reaching the thalamus, and since suppressor discharges are produced by these impulses,[13] it follows that there should be a continuous activity of the suppressor strips. It is proposed that this continuous suppressor activity results in a high threshold of the thalamic perceptive centers. This high threshold performs two basic functions: (*a*) When maintained, it prevents impulses from reaching the consciousness, and (*b*) when decreased, it permits impulses to reach the consciousness.

SCHEMATIC PRESENTATION OF SENSORY PERCEPTION

On these premises, the following mechanism of normal sensory perception is proposed. Diagrams illustrate the mechanism schematically. The right hemisphere is indicated in solid line; the left, in dotted line. The number of arrow points indicates the intensity of the impulses.

Chart 1.—Stimuli are continuously being transmitted to both thalami (arrows *1,1'*). These impulses are referred to the sensory cortices (arrows *2,2'*) and to the cortical association areas for evaluation (arrows *3,3'*). When the impulse pattern is not considered important, activation of the suppressor system is maintained (arrows *4,4'*); suppressor impulses keep the thalamic threshold high, and no perception occurs (arrows *5,5'*). Suppressor impulses are transmitted to the contralateral hemisphere (arrows *6,6'*), and suppressor impulses are received from the contralateral hemisphere (arrows *7,7'*), probably via the corpus callosum fibers. This increase in suppressor activity derived from the contralateral hemisphere also raises the threshold of the thalamic perceptive centers.

13. Dusser de Barenne and others.[11] Gellhorn.[10] Barker and Gellhorn.[12]

Chart 2.—When the first portion of a new stream of impulses (arrow *1″*) is considered important enough by the cortical association areas (arrows *2″* and *3″*), impulses to a certain area of the suppressor system are diminished (arrow *4″*); suppressor activity is reduced to a corresponding thalamic perceptive area (arrow *5″*); the threshold of

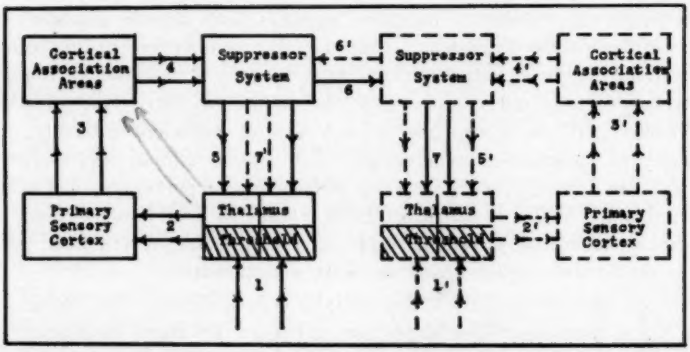

Chart 1.—The continuous flow of sensory impulses (arrows *1,1′*), having been evaluated by the cortical sensory system (arrows *2,2′3,3′*), is prevented from registering in the consciousness by continuous suppressor activity (arrows *5,5′7,7′*), which maintains a high thalamic threshold.

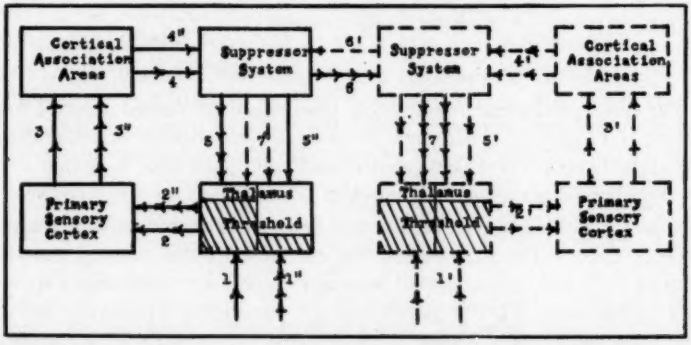

Chart 2.—Stimuli being perceived in a portion of the right thalamus as a result of a new volley of impulses from the periphery (arrow *1″*), which has automatically reduced the suppressor activity (arrow *5″*) to the appropriate thalamic center. Other stimuli (arrows *1, 1′*) are not registering.

that area is decreased, and the succeeding impulses (arrow *1″*) are now perceived by the thalamus. Suppressor activity is increased in the remainder of the cortices, both ipsilateral and contralateral (arrows *4,5,6,7*), to eliminate competing impulses by raising the threshold of corresponding thalamic centers.

Chart 3.—Another manner of altering the threshold of the thalami is through attention. The increase of auditory or visual acuity by concentration of attention, even though the stimuli themselves have not changed in intensity, is a common example. In this situation the cortical association areas initiate the diminution of excitation of the suppressor strips in a certain field (arrow *4″*). The flow of suppressor impulses to the specific thalamic center is decreased (arrow *5″*); the threshold is lowered, and perception of previously subliminal impulses (arrow *1*) can occur. The removal of attention from the other sensory fields results in a concomitant increase in threshold of these thalamic centers, which facilitates the accuracy of perception by elimination of competing impulses (arrows *5* and *6*).

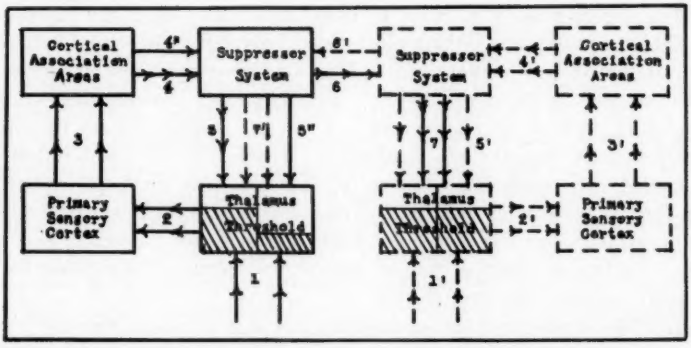

Chart 3.—Attention initiating perception of previously subliminal stimuli (arrows *1,1′*) by diminishing suppressor activity (arrows *4,″5″*) to the appropriate thalamic center. Suppressor activity is increased to the other centers (arrows *5,6,7*).

COMMENT

Comment.—It is proposed that the thresholds of the thalamic perceptive centers are maintained at a high level by continuous suppressor discharges which accompany the continuous inflow of sensory impulses. A certain pattern of stimuli may result automatically in reduction of suppressor discharges to a particular field, lowering of the threshold of the thalamic center and perception of the stimuli. Attention may also accomplish this lowering of threshold of thalamic centers. During perception suppressor discharges are increased to the remaining thalamic centers to eliminate competing impulses.

These proposals are compatible with the opinions expressed by Head, Holmes and Foerster [14] that the corticothalamic pathways inhib-

14. Head and Holmes.[8] Cited by Fulton.[4]

ited the thalami and with Brouwer's suggestion that the corticothalamic pathways modified the sensitivity of the primary receptive centers, rendering them more susceptible to incoming impulses.

SENSORY EXTINCTION

One of the phenomena of sensation which indicates that an inhibitory influence is produced by stimuli on other stimuli is the sensory extinction accompanying bilateral simultaneous stimulation. In 1900 Oppenheim,[15] in his textbook, related that in some cases in which there was no evident sensory deficit on unilateral testing, bilateral simultaneous stimulation was not perceived on one side. He reported this for vision and somatic sensation and attributed the phenomenon to inattention.

Poppelreuter in 1917, Head in 1926, Riddoch in 1935 and Akelaitis in 1942 reported cases of this phenomenon involving the visual spheres and attributed it to inattention.[16] This syndrome remained a curiosity until the work of Bender in 1945.[17] Bender's cases showing the extinction, as he termed the phenomenon, of somatic sensation were the first reported since Oppenheim's publication. Bender, in his latest report,[18] concluded that the holistic theory of Goldstein was the best explanation for the syndrome, and that the reactions of the organism depended not on excitation of single receptor fields but on a total pattern of excitation. Extinction resulted from an apparent imbalance of forces between damaged and less damaged cortex.

In 1946 Reider [19] reported several cases and proposed that the phenomenon depended on a physiologic suppressor action on damaged sensory cortex exerted by normal or less damaged tissue when stimulated. He postulated that this suppression would be correlated with the suppressor strips.

PRESENT STUDY

In the past year I have observed 12 cases in which the phenomenon of sensory extinction occurred. They constituted about one third of the cases in which there was evidence of sensory loss from cerebral lesions.

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15. Oppenheim, H.: Diseases of the Nervous System, translated by E. E. Mayer, Philadelphia, J. B. Lippincott & Company, 1900, p. 59.

16. Cited by Bender and Furlow.[17]

17. Bender, M. B., and Furlow, L. T.: Phenomenon of Visual Extinction in Homonymous Fields and Psychologic Principles Involved, Arch. Neurol. & Psychiat. **53**:29 (Jan.) 1945.

18. Bender, M. B.: Extinction and Precipitation of Cutaneous Sensations, Arch. Neurol. & Psychiat. **54**:1 (July) 1945. Bender, M. B.; Wortis, S. B., and Cramer, J.: Organic Mental Syndrome with Phenomena of Extinction and Allesthesia, ibid. **59**:273 (March) 1948.

19. Reider, N.: Phenomena of Sensory Suppression, Arch. Neurol. & Psychiat. **55**:583 (June) 1946.

20. Footnote deleted by author.

The lesion in 1 case was a venous vascular anomaly and was verified at operation. Of the other cases, in which the patients are still alive, the lesions were considered to have been cerebral emboli from the heart, in 2 cases, and cerebral thromboses due to arteriosclerosis in the remaining 9 cases, the thrombosis being primary in 6 cases and secondary to hypertensive vascular disease in 3 cases.

The distribution of the types of extinction was as follows:

Number of Cases	Field of Extinction	Side of Extinction	
		Left	Right
1	Somatic [21]; visual; auditory	1	0
2	Somatic; visual	1	1
6	Somatic	4	2
3	Visual	2	1

In all of the cases extinction was elicited by the Oppenheim technic—bilateral simultaneous stimulation of symmetric areas with similar stimuli. But extinction was easily elicited by a number of other technics. The stimuli did not have to be similar. For example, passive movement on the intact side could cause extinction of appreciation of pinprick, touch or vibration on the defective side. In fact, almost any type of stimulus to the intact side sufficed. This nonspecificity of inhibiting sensation was conspicuous in 2 cases, in which somatic stimuli caused extinction of visual stimuli. Likewise, the areas stimulated did not have to be symmetric. Stimuli to the hand could produce extinction in the contralateral face, hand, and foot, and even the eye in some cases. Unilateral double stimulation did not result in extinction. The stimuli had to be simultaneous and bilateral in these cases to produce extinction.

The superficial sensations of light touch and pain were more susceptible to extinction, whereas the deep sensations of deep pain, vibration and position sense were less liable, deep pain not showing extinction in any of the cases. The discriminative sensations of graphesthesia, stereognosis and two point discrimination were usually so defective on unilateral stimulation that they were considered nonfunctioning and were excluded from the study unless definitely perceived on unilateral stimulation.

In 6 of the cases there was definite evidence that with repeated stimulation or concentration of attention the extinction phenomenon would disappear and both stimulations be perceived. In 2 cases attention would occasionally prevent extinction on the first double stimulation, but in the remaining cases the first bilateral stimulation was invariably not perceived, regardless of the concentration of attention directed

21. Somatic sensation refers to the exteroceptive and interoceptive sensations from the body other than the special senses of vision, hearing, taste, smell and equilibrium.

in that sensory field. The extinction ceased promptly with discontinuance of bilateral stimulation, although in 2 cases prolongation of the extinction was evident at some time during the illness.

One observation was of special interest. The patient had the spontaneous pain of the thalamic syndrome with analgesia of the hand. This pain would disappear when the intact side of the body was even lightly stimulated, and the pain did not reappear for several seconds after discontinuance of such stimulation.

After study of these cases, the detailed reports of 4 of which are included in this paper, I am of the opinion that a physiologic concept, similar to that of Reider, best explains the process. The following mechanism of extinction is suggested:

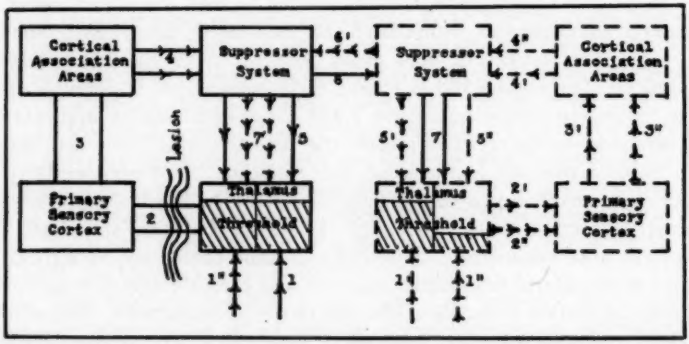

Chart 4.—Bilateral simultaneous stimulation (arrows *1″*), the left thalamus perceiving the stimuli and sensory extinction occurring on the right, as the result of a lesion in the thalamocortical projection and a summation of ipsilateral (arrow *5*) and contralateral (arrow *7′*) suppressor activity.

In parietal lesions the thalamocortical and parietal suppressor projections are usually damaged together (chart 4). Since there are suppressor projections from the frontal, occipital and temporal lobes as well, impulses still reach the suppressor system. Investigators [22] have shown that stimulation of any single suppressor strip could activate the whole suppressor system of both the ipsilateral and the contralateral hemisphere. The threshold of the thalami thus is still maintained at high level by the continuous flow of suppressor activity. However, since there is an interruption of the thalamoparietal pathways (arrow *2*), the usual mechanism of lowering the threshold automatically does not function (arrows *4″*, *5″*). To be perceived, stimuli must be much greater in intensity than usual, giving the characteristic diminution of

22. Dusser de Barenne and others.[11] Gellhorn.[10] Barker and Gellhorn.[12]

all sensation found with parietal lesions. It is thus proposed that a high threshold for sensation occurs in cases of parietal lesions, owing to persistent suppressor activity.

As previously mentioned, any stimulation produces contralateral (arrows *7,7'*), as well as ipsilateral (arrows *5,5'*), suppression. The increase in contralateral suppressor activity ordinarily is not sufficient to be recognized. However, when the threshold for perception is high, as is postulated in the case of parietal lesions, bilateral simultaneous stimulation may result in enough summation of suppressor discharges, ipsilateral and contralateral in origin, to increase further the threshold of the thalamus so that no perception occurs on the involved side and "sensory extinction" occurs. Thus, it is proposed, the requirements for extinction to occur are (*a*) a high threshold for sensation for one thalamic center and (*b*) a summation of suppressor discharges to increase further this threshold during bilateral simultaneous stimulation.

Since attention can lower the threshold in the normal sensory mechanism, it should function similarly in sensory extinction. Theoretically, focusing the attention on the involved side should diminish the impulses activating the suppressor strips (arrow *4*) and the amount of suppressor activity should decrease (arrow *5*), resulting in sufficient lowering of the threshold that the stimuli are perceived and extinction no longer occurs. In actuality, this overcoming of the extinction by attention was found to be true in 6 cases of this series. Three such cases are included in the case reports that follow.

A lesion close to the thalamus could conceivably involve most of the converging suppressor projections (arrows *5,7'*), so that little suppression would be possible. The thalamic threshold would then be very low, producing the uninhibited "excessively reacting" thalamus of Head and Holmes.

REPORT OF CASES

CASE 1.—A man aged 72 noted in June 1948 that his left foot began to drag. This weakness cleared up in a few days. In July 1948 he awoke from sleep and discovered that the whole left side of his body was numb and paralyzed.

One week later he was hospitalized. Physical examination revealed nothing abnormal except for gynecomastia. The blood pressure was 140 systolic and 90 diastolic. Routine examinations of the blood and urine, roentgenographic examination of the chest and skull and examination of the spinal fluid revealed nothing abnormal. The electroencephalogram revealed pronounced asymmetry of amplitude with the tracing from the right hemisphere practically flat.

Neurologic examination disclosed the following abnormalties on the left side: weakness of movements of the shoulder, elbow, hip and knee; paralysis of movement of the foot and hand; decreased muscular tone; exaggerated tendon reflexes; absence of superficial abdominal reflexes; presence of the Hoffmann, Chaddock and Babinski signs; absence of conjugate deviation of the eyes to the left, both volitional and reflex, and facial weakness of central type.

Sensory examination revealed that light touch, vibration and position sense, stereognosis, two point discrimination and graphesthesia were all diminished on

the left. There were analgesia over the upper limb and hypalgesia over the face and lower limb. No delusion of body scheme or somatic sensory suppression was found. The patient could perceive movement, light and the shape and color of objects in the left homonymous field; but when a stimulus was given in the right field nothing was discerned in the left field. Attention did not affect the extinction. The extinction occurred immediately with the first bilateral stimulation and ceased promptly with the withdrawal of the stimulus from the right field.

In the succeeding four weeks the disturbance of lateral conjugate movement improved to a point where he could move his eyes to the left with effort. The visual extinction persisted. He then began to note spontaneous pains in the left limbs.

Examination at that time, September 1948, showed that when bilateral stimulation was made with passive movement, vibration and light touch the stimulus on the left was not perceived. Appreciation of pinprick in the foot and face also showed extinction. Deep pressure and deep pain sensation did not. Of interest was the fact that the spontaneous pain in the left arm and leg disappeared during stroking of the right sole for the duration of the stimulation and several seconds afterward. Passive movement of the toes and fingers and repeated pinprick and touch stimuli produced similar extinction of the spontaneous pains.

The sensory extinction was manifested as long as the stimuli were simultaneous. The areas stimulated did not have to be symmetric. Stimulation of the right hand suppressed sensation from the left side of the face and the left arm or leg. The same applied to other combinations. Ipsilateral double stimulation did not result in sensory extinction. He did not show any prolongation of sensory extinction in the method used. Repeated stimulation of the right side alone or of both sides at the rate of one stimulus per second was reported as being felt only on the right. When the next stimulus was applied (one second interval) to the left side alone, it was immediately perceived on the left. There was no delay in the extinction, nor did attention affect the results. The sensations did not have to be identical to produce the extinction. Appreciation of pinprick on the left was suppressed by touch stimuli on the right. Similarly, vibration or passive movement on the right would suppress perception of pinprick or touch on the left.

The patient also showed the extinction in the auditory sphere. Hearing on bilateral stimulation with C-1 tuning forks (128 double vibrations) outside the ears was reported only on the right even when attention was focused on the left. Single stimulations were lateralized correctly.

Case 2.—A man aged 53 was known to have had hypertensive vascular disease since 1939. Since 1942 he had had several episodes of dizziness, transitory numbness and loss of motor power. In 1944 this weakness affected the right side, and his speech was thick for several days. On two occasions the left side was affected. In June 1948 he had a severe gastric hemorrhage. Two weeks later he had a jacksonian seizure involving the left side, after which he lost his speech and had several crying spells. In the succeeding months his speech improved but had not returned to normal, and the emotional lability remained.

Routine laboratory tests, including roentgenographic examination of the chest, skull and gastrointestinal tract, were noncontributory. The results of physical examination were essentially normal except for a blood pressure that fluctuated from 200 to 120 systolic and 150 to 80 diastolic. The electroencephalogram showed diphasic spikes in the leads from the right occipital and parietal regions.

Neurologic examination in September 1948 revealed the following abnormalities: mild dysarthria, mild semantic aphasia, mild defect in language formulation and dyslexia. Writing was excellent in form but showed the defect of language

formulation. There was weakness of the left foot and hand. Rapid alternating movements were executed poorly with the left hand and foot, as well as with the tongue, jaws and lips. The Hoffmann, Chaddock and Babinski signs were elicited on the left. Hypalgesia on the left side, including the face and trunk, was evident. Vibration sense was also diminished on the left side. Position sense, graphesthesia, stereognosis, two point discrimination and light touch sense were intact and equal on the two sides.

With bilateral stimulation extinction was present for pain and touch sensation and for graphesthesia. This was the only case of this series in which extinction of modalities occurred which were not found to be diminished on unilateral stimulation, i. e., touch sense and graphesthesia.

There was also extinction in the left homonymous visual field. In the upper left quadrants the patient could perceive motion and form by concentrating after six to seven seconds of bilateral stimulation. No amount of concentration could produce perception in the left inferior quadrants. The extinction was immediate, and there was no poststimulation suppression.

Follow-up examination in October 1948 revealed that the week previously he had had pains in the whole left side for several days. Examination disclosed progression of the sensory loss. All sensation was now diminished on the left side. Extinction was present for passive movement, as well as for appreciation of touch and pinprick and graphesthesia. However, when he concentrated on the left side and the bilateral stimulations were repeated four to five times, he could overcome the suppression. A single set of stimuli was invariably missed, regardless of the amount of concentration. On the face there was extinction of appreciation of pinprick, but not of light touch. The extinction of vision in the left homonymous field was still present, but by concentrating he could perceive motion and form in both the superior and the inferior portion of the field, provided there was stimulation for at least three seconds.

As in case 1, the stimuli did not have to be identical or the areas symmetric to produce the extinction. Almost any stimulus on the right would suffice. The same sensations on the left were suppressed with the technic of similar stimuli and symmetric areas as with the dissimilar technic of stimuli and asymmetric areas.

CASE 3.—A man aged 61 had known of his hypertension for twelve years but had been asymptomatic except for occipital headaches. In September 1948, while peeling vegetables, he noted numbness of the right hand. Three hours later he realized that he could not move his right hand. During the next week, weakness, clumsiness and numbness appeared in the right leg as well. Along with these symptoms he noted that it was difficult for him to think of the words to say and how to say them. He noted rapid improvement in his condition during the week prior to examination.

The results of physical examination were normal except for a blood pressure of 170 systolic and 140 diastolic. Routine laboratory examinations of the blood and urine and roentgenographic examination of the chest and skull revealed nothing abnormal. The electroencephalogram showed high voltage, wide-based spikes in both parietal areas, particularly on the left.

Neurologic examination revealed the following abnormalities: mild semantic aphasia; mild formulation aphasia; dyslexia; complete agraphia; moderate weakness and severe apraxia of the right hand; presence of Oppenheim and Babinski signs on the right; absence of superficial abdominal reflexes, and hyperactivity of the deep reflexes on the right.

All sensation was diminished on the right side, including the face. Single stimuli were perceived readily on the right. On bilateral simultaneous stimulation

with pinprick, touch or passive movement, only the stimuli on the left were perceived. There was fluctuation of the extinction. After six to seven seconds of repeated testing, he tended to perceive both stimuli. After an interval of several minutes, the extinction was again persistent for four successive double stimulations in the same areas.

One week later the extinction of perception of pinprick in the foot still fluctuated, but not that of the sensations of touch or passive movement, which were persistent. In the hand he showed prolonged extinction for four seconds on several trials; i. e., after cessation of stimulation on the left, the next four stimulations on the right were not perceived at all. On two occasions, after several bilateral stimulations in which only the stimuli on the left were reported, stimulation of the right side alone was reported as on the left for the next four stimuli, and then as on the right. This is the only case of the series in which these phenomena of allesthesia and prolonged extinction occurred together. The suppression occurred with dissimilar stimuli and asymmetric areas, as in cases 1 and 2. Ipsilateral suppression was not observed.

Case 4.—A man aged 41 was originally hospitalized in October 1947 because of repeated convulsions on the left side. Ventriculograms had shown displacement of the right lateral ventricle. A craniotomy revealed a mass of veins containing arterial blood at the junction of the parietal and the occipital lobe. The center of the mass of vessels was softened and discolored. The anomalous vessels were coagulated and the softened areas removed. He made a complete recovery. An angiogram of the internal carotid artery revealed no residua of the anomaly. Visual fields taken in the department of ophthalmology in December 1947 were normal.

In August 1948 the patient returned to the hospital because of abdominal complaints. A barium sulfate meal disclosed pylorospasm and a marked delay in the emptying time of the stomach. The electroencephalogram revealed a focus of slow waves in the right occipital area. Visual fields taken by perimetry were normal.

Neurologic examination in August 1948 revealed the following abnormalities: absence of the plantar response bilaterally, and dyscalculia and extinction of vision in the left homonymous field on bilateral stimulation. A search for other sensory defects revealed nothing. The extinction of vision occurred immediately on bilateral stimulation, with either eye separately or with both eyes, as long as the right field of one was stimulated simultaneously with the left field. The left image was perceived as soon as the image in the right field was removed from view. Even when his attention was focused on the left field, the extinction occurred. There was no fading of form or color in the left field on unilateral stimulation. The patient had not noticed any visual disturbances in reading or in his usual activities.

One month later he was reexamined. He had been under treatment with diphenylhydantoin hydrochloride, 0.4 Gm. daily. The pylorospasm and impaired motility of the stomach were no longer evident roentgenologically. The dyscalculia had almost disappeared. In the upper left quadrant of the left visual field he could occasionally perceive bilateral stimulation, but after three to four seconds of bilateral stimulation the image on the left would fade. Sometimes the extinction occurred immediately, and after seven to eight seconds, by concentration, he could discern movement on the left. Extinction was more frequently present when moving objects were used in the right field of vision and stationary objects in the left field. In the lower quadrant of the left field the extinction remained consistent without fluctuation.

One of the striking examples of extinction was observed when somatic stimuli on the right resulted in suppression of vision in the left homonymous field. When the right hand was stimulated with repeated passive movement, touch or pinprick, a moving object or a light shining in the left field alone was not perceived for six to seven seconds, even though his attention was focused in that field. Stimuli in the leg gave the same result but the extinction lasted only three to four seconds. Somatic stimuli in the left limbs did not result in extinction. During intense concentration, as in performing tasks in mental arithmetic, unilateral stimulation in the left field was still perceived.

SUMMARY

The develoment of the suppressor strip mechanism in the field of sensation is summarized.

It is suggested that activity of the suppressor strips regulates the threshold of the thalamic perceptive centers and constitutes one of the fundamental mechanisms of sensory perception.

The history of the syndrome of sensory extinction is reviewed.

Results in a series of 12 cases of sensory extinction are outlined.

(*a*) Sensory extinction was observed to be produced by dissimilar stimuli from asymmetric areas, as well as by the Oppenheim technic of similar stimuli in symmetric areas.

(*b*) Attention was found capable of overcoming the sensory extinction in 6 cases.

It is proposed that the essential role of the stimulus on the intact side in sensory extinction is to produce an increase in contralateral suppressor activity.

The conclusion is reached that sensory extinction occurred when there were a high threshold for perception and a summation of suppressor activity from two simultaneously administered stimuli.

Reports of 4 cases illustrating the various types of sensory extinction are given in detail.

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COURSE AND SYMPTOMS OF PROGRESSIVE INFANTILE MUSCULAR ATROPHY

A Follow-Up Study of One Hundred and Twelve Cases in Denmark

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PROGRESSIVE infantile muscular atrophy was first described by Werdnig [1] and Hoffmann [2] about fifty years ago. This disorder is defined as a hereditary familial degeneration of the motor cells in the anterior horns of the spinal cord causing progressive atrophy and paralysis of the skeletal muscles. The atrophy begins in the muscles of the back and in the proximal muscles of the limbs and spreads gradually to the whole body. Life is threatened when the nerve cells supplying the respiratory muscles are affected, particularly when this involvement is followed by infection of the respiratory tract.

Up to the time of this report, approximately 200 cases, occurring in about 120 families, have been reported. However, the reader will still find the best description of the disease in Hoffmann's papers. Many later single observations and short series of cases have contributed to our knowledge of the disease and its relation to Oppenheim's [1] amyotonia congenita (Batten,[3] Krabbe,[4] Slauck,[5] Greenfield and Stern,[6] Schild-

1. Werdnig, G.: Zwei frühinfantile hereditäre Fälle von progressiver Muskelatrophie unter dem Bilde der Dystrophie, aber auf neurotischer Grundlage, Arch. f. Psychiat. **22**:437, 1891; Die frühinfantile progressive spinale Amyotrophie, ibid. **26**:706, 1894.

2. Hoffmann, J.: Ueber chronische spinale Muskelatrophie im Kindesalter auf familiärer Basis, Deutsche Ztschr. f. Nervenh. **3**:427, 1893; Weitere Beiträge zur Lehre von der hereditären progressiven spinalen Muskelatrophie im Kindesalter, ibid. **10**:292, 1897; Dritter Beitrag zur Lehre von der hereditären progressiven spinalen Muskelatrophie im Kindesalter, ibid. **18**:217, 1900; Ueber die hereditäre progressive spinale Muskelatrophie im Kindesalter, München. med. Wchnschr. **47**:1649, 1900.

3. Batten, F. E.: Progressive Spinal Muscular Atrophy of Infants and Young Children, Brain **33**:433, 1910-1911.

4. Krabbe, K. H.: Congenital Familial Spinal Muscular Atrophies and Their Relation to Amyotonia Congenita, Brain **43**:166, 1920.

5. Slauck, A.: Ueber Myatonia congenita und infantile progressive spinale Muskelatrophie, Deutsche Ztschr. f. Nervenh. **67**:1, 1921.

6. Greenfield, J. C., and Stern, R. O.: The Anatomical Identity of the Werdnig-Hoffmann and Oppenheim Forms of Infantile Muscular Atrophy, Brain **50**:652, 1927.

knecht,[7] de Lange,[8] Karlström and Wohlfart,[9] Hanhart[10] and others). Most textbooks give the impression that this disease is extremely rare. According to my experience, however, this disorder should not be considered uncommon. During the last five years I have personally observed about 20 new cases. At the same time, it is likely that in many present cases the disease goes undiagnosed or is treated as rickets or some other condition. In spite of the muscular weakness, infants with progressive muscular atrophy appear healthy and well nourished. An early and surprising death following an apparently mild infection of the respiratory tract often eliminates the possibility of clinical diagnosis.

MATERIAL OF PRESENT STUDY

This study is the first analysis of a large number of cases of progressive infantile muscular atrophy followed through several years. It includes recent

TABLE 1.—*Primary Diagnoses in 112 Cases of Progressive Infantile Muscular Atrophy*

Diagnosis	Number of Cases
Progressive infantile muscular atrophy	40
Amyotonia congenita	38
"Abiotrophic disorder"	2
Atypical myopathy	7
Mental deficiency	1
Rickets and tetany	2
Hematomyelia	1
Injury of nerve plexus at birth	1
Poliomyelitis	1
Pareses of lower extremities	1
Condition undiagnosed (sibling cases)	18

cases investigated by newer methods, such as biopsy of muscle and electromyography. The clinical material comprises in all 112 cases discovered in Denmark during the last forty years.[11]

7. Schildknecht, O.: Ueber die frühinfantile, progressive, spinale Muskelatrophie (Werdnig-Hoffmann) und ihre Beziehung zu Myotonia congenita (Oppenheim), Deutsche Ztschr. f. Nervenh. **134**:163, 1934.

8. de Lange, C.: Studien ueber angeborene Lähmungen bzw. angeborene Hypotonie, Acta pædiat. **20** (supp. 3):1, 1937.

9. Karlström, F., and Wohlfart, G.: Klinische und histopatologische Studien über infantile spinale Muskelatrophie (Oppenheim'sche und Werdnig-Hoffmann'sche Krankheit), Acta psychiat. et neurol. **14**:453, 1939.

10. Hanhart, E.: Die infantile progressive spinale Muskelatrophie (Werdnig-Hoffmann) als einfachrezessive, subletale Mutation auf Grund von 29 Fällen in 14 Sippen, Helvet. pædiat. acta **1**:110, 1945.

11. Some of the cases have already been published by the following authors: Wimmer (Arch. f. Psychiat. **42**:960, 1906), Krabbe,[4] Gjørup and Schrøder (Acta pædiat. **18**:211, 1935), Hilden (Nord. Med. **9**:412, 1941) and Oluf Andersen (Ugesk. f. læger **101**:606, 1939).

As shown in table 1 and reported in a previous paper (Brandt [12]), the original diagnosis of progressive infantile muscular atrophy had been made correctly in 40 of the cases. In 38 cases the original diagnosis had been amyotonia congenita of Oppenheim (or a similar diagnosis indicating a nonprogressive condition); in 2 cases, an "abiotrophic disorder," and in 7 cases, progressive myopathy. In the remaining 25 cases the patients were siblings of the 87 patients just mentioned; either they had never been studied intensively, or their condition had been recorded as mental deficiency, rickets with tetany, hematomyelia, injury of the spinal root plexus at birth, poliomyelitis or "paralysis."

I have personally examined 31 of the 112 patients. Eleven were older children, found during the follow-up study; 20 were new patients, observed through the last five years. The remaining 81 patients I have not seen myself, but details of great value regarding the symptoms and course of the disease were obtained in follow-up interviews with the parents and, in some cases, from records of other clinics or institutes to which the child was admitted after the first diagnosis was made.

The reclassification diagnosis [13] used, namely, progressive infantile muscular atrophy, covers only the clinical picture, which in my experience is very similar to the commoner spinal type, originally described by Werdnig and Hoffmann, and to the rare myopathic type, described by de Lange, Menges,[14] Fiore,[15] Finkelnburg [16] and Keferstein.[17] Muscle biopsy and/or electromyography are usually necessary to make a clearcut differentiation of these types before death.

In this report, the chief emphasis will be on the clinical course and symptoms of the disease. In other publications, further details of the pathologic features, as well as of the results of genetic studies,[18] will be given.

RESULTS

Sex Distribution.—The series includes 57 boys and 55 girls, thus indicating an equal distribution of males and females.

Age at First Manifestation of Symptoms (table 2).—Muscular weakness started before the end of the first year of life in 97 patients (87 per cent) and within the first six months in 73 patients (65 per cent) and was observed just after birth in 41 infants (35 per cent).

12. Brandt, S.: Amyotonia Congenital Symptom and Not Separate Disorder: Follow-Up Study of One Hundred and Thirty-One Infants with Muscular Hypotonia, J. Child, Psychiat. **1**:266, 1949.

13. Details of this reclassification and additional information will be published later in a monograph entitled "Werdnig-Hoffmann Progressive Infantile Muscular Atrophy."

14. Menges, O.: Ein Beitrag zur Pathologie der Myotonia congenita, Deutsche Ztschr. f. Nervenh. **121**:240, 1931.

15. Fiore, G.: Atonia muscolare congenita e distrofie muscolari fetali, Riv. di clin. pediat. **25**:319, 1927.

16. Finkelnburg: Anatomischer Befund bei progressiver Muskeldystrophie in den ersten Lebensjahren, Deutsche Ztschr. f. Nervenh. **35**:453, 1908.

17. Keferstein, G.: Ueber die progressiven Muskelatrophien, Dissertation, Göttingen, 1894.

18. Brandt, S.: Hereditary Factors in Infantile Progressive Muscular Atrophy, Am. J. Dis. Child. **78**:226 (Aug.) 1949.

A history of absence of fetal movements was obtained from 12 mothers and of decreasing movements by 4 others, thus suggesting the prenatal beginning of the disease.

Course.—When severe paralyses were present at birth or soon after, further progress was difficult to demonstrate until the muscles of the respiratory system were involved. However, in such cases single enlarged motor horn cells revealing extreme chromatolysis could almost always be observed at autopsy, in addition to a large number of small, atrophic, shrunken cells, features which point clearly to the degenerative nature of the disease.

TABLE 2.—*Age at First Clinical Manifestation in 112 Cases of Progressive Infantile Muscular Atrophy*

Age	Number of Cases		
Newborn	41	73 (65%)	97 (87%)
0- 1 month	11		
1- 3 months	14		
3- 6 months	7		
6-12 months	24		
More than 1 year	9		
Age unknown	6		

TABLE 3.—*Age at Death in 95 Cases of Progressive Infantile Muscular Atrophy*

Age	Number of Cases		
Less than 1 year	53	(56%)	76 (80%)
1- 4 years	23		
4-15 years	13		
15-20 years	6		
Age unknown	1		

In cases in which the muscular weakness was first observed several months after birth a less rapid progress was common, and in such cases the disease sometimes seemed stationary for months or years. This fact made it possible for many of the often very intelligent little patients to acquire some motor power and weight-supporting ability in those parts of their muscles that were less involved, but this apparent improvement was only temporary and was later replaced by further progression of the weakness.

Ninety-five of the 112 patients in the present series died before the present study was finished (table 3). Fifty-three (56 per cent) died before the end of their first year; 76 (80 per cent), within the first four years of life, and the remaining 18 before their twentieth year. The time of death of 1 patient could not be determined. Eight patients

(about 7 per cent) lived more than fifteen years. Of these, 6 died a few years later. The 2 oldest of the 17 patients who were still alive at the last report were 18 and 20 years old, respectively, and were both completely disabled, with extreme muscular atrophy and paralysis.

Symptoms.—A complete clinical record was available for 91 patients. Forty-five of these patients were less than 1 year old when examined. The predominance of various signs and symptoms depended to some extent on the age of the child.

In all the 45 infants less than 1 year old, universal hypotonia was found (fig. 1). Almost complete paralysis except for the muscles

Fig. 1.—Extreme universal hypotonia in a 5 month old girl observed by the author. The condition was first observed at the age of 2 months. The child died shortly after, and autopsy revealed severe atrophy of the anterior horn cells of the spinal cord. In the muscles atrophy of spinal type was found.

innervated by the cranial nerves was observed in all but 1 infant, only slight movements of the hands and feet being present. Muscular atrophy was mentioned as a sign in only 25 of the 45 infants, while loss of the knee reflex was observed in 39; no information about the knee reflex was available for 5 patients, whereas the presence of this reflex was doubtful in 1 child. Twenty-four of the 45 infants showed a remarkable deformity of the thorax due to paralysis of the intercostal muscles (fig. 2). This was accompanied by a reversed type of breathing, with protrusion of the abdominal wall during inspiration. Feebleness and weakness of the voice was found in at least 16 infants. In 15 babies

contractures in the shoulders, hands, lower portions of the arms or knees were noted. These seemed to be caused by inequality of muscle tone in antagonistic muscle groups rather than by shrinking of scar tissue, such as was found in older patients. Other symptoms noticed among these 45 infants were subcutanous infiltrative edema, found particularly on the dorsa of the feet (14 infants), increased perspiration (13 infants), hyperflexibility of joints (12 infants), fibrillation of the tongue (12 infants), constipation (6 infants), decreased skin sensibility (5 infants) and decreased electrical irritability of nerves or muscles (6 infants). Reaction of degeneration was found in only 4 infants, but in 33 infants no examination of electrical irritability was made. Some

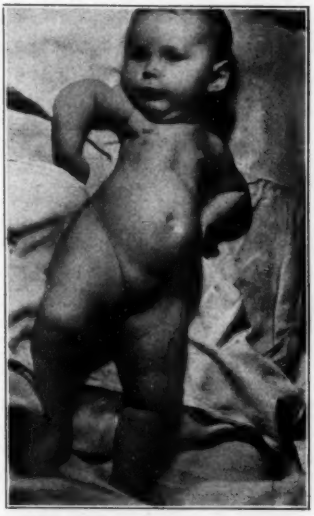

Fig. 2.—The same child as that shown in figure 1. Note posture of the limbs, deformity of the chest, protrusion of the abdominal wall and the bright, intelligent eyes.

involvement of the muscles innervated by the cranial nerves other than the hypoglossal was noticed in 17 infants, the symptoms being slightly decreased mobility of the face (in 6), distinct paralysis of the facial nerve (in 5 or 6), difficulties in swallowing (in 4) and questionable atrophy of the temporal muscles (in 2).

In children more than 1 year of age hypotonia and decrease in muscular power were less distinct than in the infant group, the predominant findings being atrophy, fibrillation or fasciculating tremor in the muscles and contractures. In this age group, because of less abundant subcutaneous fat, the prevalence of atrophy in the proximal

muscles of the limbs was easier to demonstrate. These older children sometimes learned to stand and walk a few steps but soon lost such ability. Weakness of the pelvic musculature was clearly demonstrable when the child tried to arise, it being necessary to use the upper extremities in assistance, by placing the hands on the front of the thighs and gradually moving them upward. Extreme obesity or emaciation was often found in older children; the obesity created a special problem for the relatives or nurses who had to carry the disabled patient. Mentally these children were usually normal; emotionally they were often astonishingly well adjusted to their distressing disability.

Special Examinations.—In 12 of 26 patients on whom muscle biopsies were obtained a simple atrophy was observed, including smaller or larger groups of atrophic muscle cells, scattered among other groups of muscle cells which were of normal size or slightly hypertrophied (fig. 3 *A*). According to Wohlfahrt and Wohlfart [19] this change is typical of muscular atrophy of spinal origin and is easily distinguishable from the alterations in atrophies of a dystrophic type (fig. 3 *B*), which show a diffuse mixture of normal and atrophic cells. In 5 of the patients in whom muscle biopsy revealed a spinal type of atrophy, the diagnosis was confirmed at autopsy by the finding of severe damage to the motor horn cells of the spinal cord. In 5 other patients the spinal origin of the atrophy was confirmed by electromyography, as will be explained later. In 4 patients biopsy revealed a great number of atrophic muscle cells, without any arrangement in groups or fields, but scattered diffusely among normal or hypertrophied cells (fig. 3 *B*). Proliferation of the connective tissue between the muscle cells was observed in 3 of the patients. Although this picture suggests the presence of a myopathy, it should be mentioned that autopsy in 1 of the 4 cases made it necessary to change the diagnosis to spinal atrophy. In 10 patients muscle biopsy revealed only severe atrophy, with extreme proliferation of connective tissue and fat and more or less degenerative changes in the muscle fibers, making it impossible to determine the type of atrophy.

Electromyographic studies were carried out on 19 patients with the technic described by Buchtahl and Clemmesen.[20] In each pair of electrodes one electrode was shaped like a cannula and the other was a centrally placed needle, insulated from the inner surface of the cannula. The reader is referred to the articles of Buchtahl and Clemmesen [20] for the interpretation and the clinical evaluation of this examination. For

19. Wohlfahrt, S., and Wohlfart, G.: Mikroskopische Untersuchungen an progressiven Muskelatrophien, Acta med. Scandinav., 1935, supp. 63, p. 1.

20. Buchtahl, F., and Clemmesen, S.: On the Differentiation of Muscle Atrophy by Electromyography, Acta psychiat. et neurol. **16**:144, 1941; The Electromyogram of Atrophic Muscles in Cases of Intramedullar Affections, ibid. **18**:377, 1943.

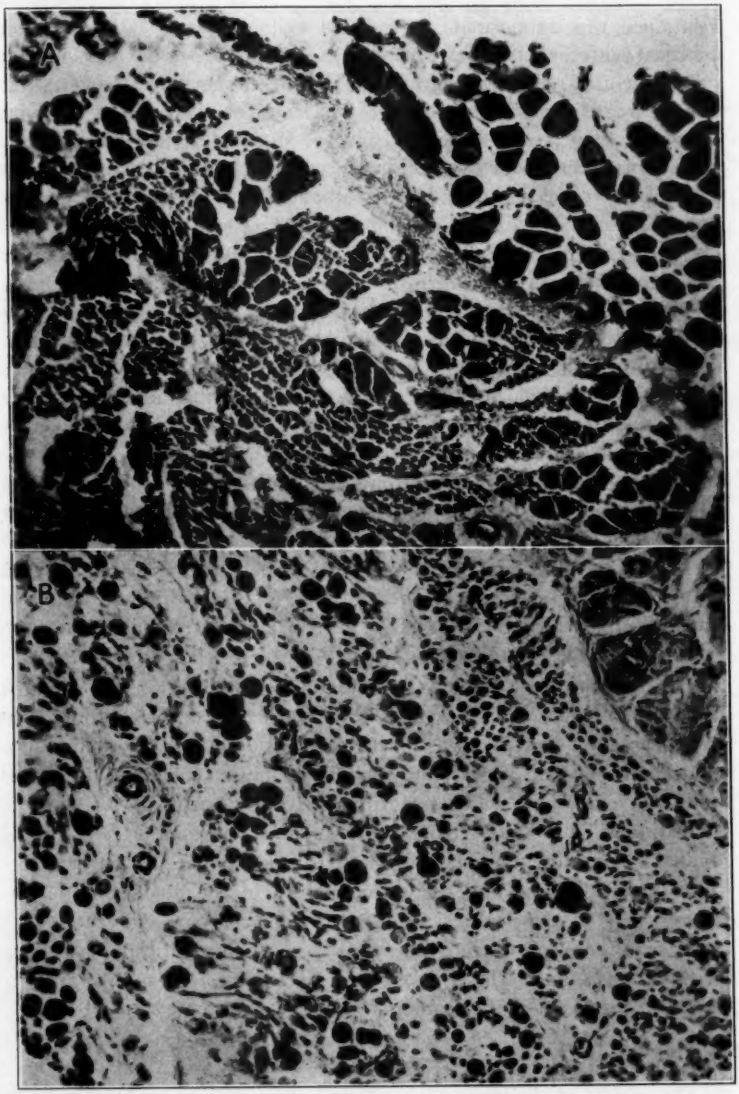

Fig. 3.—*A*, biopsy specimen from the quadriceps muscle of a 8½ month old child, showing the spinal type of atrophy, confirmed by autopsy. Hematoxylin and eosin; magnification, 150. *B*, biopsy specimen from the quadriceps muscle of a 4 week old child, showing diffuse atrophy of the type seen in the myopathies. Autopsy was not performed. Hematoxylin and eosin; × 150.

those, however, who are not familiar with these tests, it should be mentioned that in normal muscles, as well as in myopathic muscles, maximal active contraction results in a solid background of summated spike potentials ("interfering activity"), whereas in the case of destruction of a great many motor nerve cells and/or their axons maximal contraction will result in single spikes. If the degeneration is in the motor horn cells, these single spikes occur synchronously from separate pairs of electrodes. Single spikes without synchronism suggest neurogenic atrophy, either neural or spinal.

In 11 patients, from 6 months to 13 years old, complete agreement was found between the electromyographic diagnosis and the anatomic or clinical diagnosis, such as was based on biopsy, autopsy or the presence of such symptoms as muscle fibrillations or reaction of degeneration. For 10 of these 11 patients the electromyographic diagnosis was spinal, or neurogenic atrophy. In 1 patient normal innervation was found, confirming the myopathic nature of the atrophy, which the biopsy results had made probable.

For 6 patients, 5 infants from 1½ to 14 months of age and 1 child 6½ years old, the anatomic or clinical diagnosis of spinal atrophy could not be confirmed by electromyography.

In 3 cases the diagnosis of the type of atrophy was based only on the electromyogram, which showed a spinal type in 1 case and a normal innervation in 2 cases, suggestive of, but not necessarily indicating, a myopathic type of atrophy.

Other Laboratory Data.—The creatin metabolism was determined in only 9 patients. All showed an abnormal excretion of creatine, even when the age of the child was taken into consideration. Normal values for cells and protein were found for all 36 children in whom the spinal fluid was examined. The eyegrounds were normal in 27 patients studied, and the Wassermann reaction was normal in 43. In 2 children disturbing muscular fibrillations were found in routine electrocardiograms, indicating the spinal nature of the atrophy and confirming similar experiences reported by Karlström and Wohlfart.[9] Otherwise, the electrocardiogram showed no abnormalities. In 4 cases the blood was found to be Rh positive. No agglutinins could be demonstrated in the blood of the mothers.

COMMENT

The results of this analysis confirmed the impression obtained from a study of the literature, that is, that progressive infantile muscular atrophy has frequently been considered amyotonia congenita. This may be explained by the fact that slight improvement in muscular power observed in a hypotonic infant is attributed to healing of the pathologic

condition. This conclusion, however, is justifiable only when the improvement is steady and lasting. Another cause of misdiagnosis in such cases is the belief that no distinction is possible between amyotonia congenita and progressive infantile muscular atrophy and that therefore the two terms can be used synonymously. Some authors reserve the term amyotonia congenita for cases of progressive infantile muscular atrophy in which it is supposed that degeneration has reached its maximum before birth and the condition in the newborn baby is considered a residual defect. Grinker [21] tried to find histologic support for this theory at autopsies. However, such evidence is not conclusive, for postnatal onset and a rapid downhill course may be reported in cases without histologic evidence of progression. In fact, without taking such clinical data into consideration, Grinker placed 2 of Hoffmann's cases in the group which he, on the basis of histologic study, named amyotonia congenita!

The figures in table 2 show that progressive infantile muscular atrophy is manifested at birth in more than one third of all cases. In these cases of the congenital type the diagnosis of amyotonia congenita could be considered, but the distressing figures indicating the essentially steady downhill course of the disease give no support to such a diagnosis. In a previous paper (Brandt [12]), the existence of amyotonia congenita as a separate disease was questioned, and it was concluded that the separation was untenable; however, the classification is acceptable as a symptomatic diagnosis, which should be followed by etiologic studies in each case.

The importance of muscle biopsies and electromyography as diagnostic aids has been confirmed by this study. Muscle biopsy is most valuable in the case of infants, because the disease has existed for a rather short period and extensive proliferation of connective tissue has not yet occurred. Electromyography is useful as soon as the child has reached an age at which muscle contraction with maximal force can be performed on request. The spinal type of atrophy is by far the most frequent, but occasionally cases are found in which the disease is best classified as a myopathic type with a course and clinical appearance different from the general progressive myopathy of childhood, and clinically hardly distinguishable from the spinal type.

SUMMARY

One hundred and twelve cases of progressive infantile muscular atrophy occurring in Denmark during the last forty years are analyzed. The primary diagnoses are listed on table 1.

21. Grinker, R. R.: The Pathology of Amytonia Congenita: A Discussion of Its Relation to Infantile Progressive Muscular Atrophy, Arch. Neurol. & Psychiat. **18**:982 (Dec.) 1927.

No difference in sex distribution was found. In one third of all cases the disease was congenital. Transitory improvement could be observed in some patients. Only 7 per cent of all patients survived their fifteenth year of age, and these were all greatly disabled. Eighty per cent died before they were 4 years old.

Extreme hypotonia and absence of spontaneous movements were the dominant symptoms in 45 infants less than 1 year old, whereas atrophy of the proximal muscles and muscular fibrillations were particularly conspicuous symptoms in patients of the older age group.

Muscle biopsy and electromyography were important aids in an exact anatomic diagnosis; they indicated that the disease was usually of spinal origin, even if a few cases of myopathic type were found with a clinical picture hardly distinguishable from that of the spinal cases.

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INCIDENCE OF PSYCHOMOTOR EPILEPSY IN AN ARMY PSYCHIATRIC CONSULTATION SERVICE

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WE HAVE been impressed by the incidence of psychomotor epilepsy in the patients seen at the neuropsychiatric consultation service of the Third Armored Division, Fort Knox, Ky. A wide variety of psychiatric conditions, particularly inadaptability and disciplinary problems, are seen in this service. Recognition of psychomotor epilepsy is felt to be important in that it is a factor in the differential diagnosis of some psychiatric syndromes. We feel that increased awareness of the variety of symptoms presented in psychomotor epilepsy and more widespread use of the electroencephalograph will result in a substantial increase in the recognition of this condition. Our experience at the consultation service illustrates this point graphically. During 1948, of 4,047 new patients seen, 94 (2.3 per cent) had a disorder diagnosed as epilepsy, and, of these, only 2 were considered to have the psychomotor type. In the first two months of 1949, 651 new patients were seen. For 34 of these (5.2 per cent) the diagnosis of epilepsy was made; 15 had psychomotor epilepsy alone, and 4 had mixed epilepsy (psychomotor and grand mal). During 1948 this service did not have access to the electroencephalograph. The doubling of the incidence of epilepsy appears to be directly attributable to the finding of cases of psychomotor epilepsy which presumably were previously missed.

Patients with the presenting complaint of "absentee without official leave (AWOL)," "nervousness," "enuresis," "irrational behavior" or "behavior problem," and whose condition fell within the clinical picture of psychoneurosis (especially anxiety and dissociation), pathologic personality or psychosis, revealed on careful questioning a history of psychomotor seizures. For many of these patients psychomotor

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The electroencephalograms were recorded at the Louisville General Hospital, Louisville, Ky., and were interpreted by Dr. Ephraim Roseman, Professor of Neurology, University of Louisville School of Medicine.

epilepsy proved to be the major diagnosis. For the remainder it was felt to be a factor in the genesis of the personality disturbances.

According to Gibbs,[1] psychomotor epilepsy is characterized by "periods of confusion with incoordination and apparently purposeful movements." Lennox [2] defined the psychomotor attack as a "period of amnesia without convulsive movement other than possibly some tonic rigidity of muscles." From our observations, we would define psychomotor epilepsy somewhat more broadly, as a condition characterized by periodic episodes of uncontrollable behavior without convulsive movements, associated with cerebral dysrhythmia. During the attack the patient usually appears to be conscious, and he may or may not have amnesia for the episode. Psychomotor epilepsy may appear as a solitary epileptic phenomenon or in conjunction with other forms of epilepsy.

Roseman [3] found that the incidence of psychomotor epilepsy was 15 per cent of all epileptic disorders, but, on reviewing his last 300 epileptic cases, he determined the incidence to be approximately 40 per cent, alone or in combination with the grand mal or petit mal forms.[4] He attributed the increase in estimated incidence to heightened awareness of the condition and the aid rendered by the electroencephalograph, especially with the use of sleep records. Of the 34 epileptic patients we have seen, 19 (56 per cent) had the psychomotor form, which occurred either alone, as the only epileptic manifestation, or in conjunction with grand mal. This relatively high incidence of psychomotor epilepsy may be due to several factors in the Army situation. Psychomotor epilepsy seems to be most prevalent in the 20 to 40 year age group,[5] and this is precisely the group seen in the service. Many abnormal personality types are referred to an Army consultation service; the frequent occurrence of personality disorder in patients with psychomotor epilepsy has been indicated by Gibbs and associates.[5] In addition, psychomotor epilepsy is more difficult to detect than is grand mal in preenlistment and preinduction medical examinations.

The electroencephalogram in psychomotor epilepsy characteristically shows "discharges of flat-topped 4 per second waves, together with

1. Gibbs, F. A.: New Drugs of Value in the Treatment of Epilepsy, Ann. Int. Med. **27**:548-554, 1947.

2. Lennox, W. G.: Tridione in the Treatment of Epilepsy, J. A. M. A. **134**:138-143 (May 10) 1947.

3. Roseman, E.: Epileptic in the Army, Am. J. Psychiat. **101**:349-354, 1944.

4. Roseman, E., and Aring, C. D.: Epilepsy, in Progress in Neurology and Psychiatry, New York, Grune & Stratton, Inc., 1948, pp. 193-206.

5. Gibbs, E. L.; Gibbs, F. A., and Fuster, B.: Psychomotor Epilepsy, Arch. Neurol. & Psychiat. **60**:331-339 (Oct.) 1948.

high voltage 6 per second waves or discharges of irregular positive spikes," appearing in bursts.[6] Patients with a history of epilepsy are more than twice as prone to show seizure discharges during sleep as during the waking state.[7] Discharges of the psychomotor type are especially likely to be absent when the patient is awake and to be present during sleep. They can be shown to be focal particularly in the temporal area.[5]

Physical and neurologic examination of patients with psychomotor epilepsy commonly reveals no abnormality.

In the cases seen at our consultation service the diagnosis was made principally on the history. Only occasionally were patients observed during seizures. In all cases included in this report electroencephalograms were compatible with the aforementioned criteria. No sleep records were taken in this series. In view of studies indicating that psychomotor discharges are more easily detected during sleep,[5] it is possible that our reported incidence of psychomotor epilepsy would be greater had we been able to obtain electroencephalograms recorded in sleep.

The following cases are illustrative of the diagnostic problems presented.

CASE 1.—A platoon sergeant aged 27 was referred to this service because one day, when he was about to give his men physical training, he suddenly could not remember what to say, became nervous and flustered and had to stop. At the interview, he stated that after this episode he was afraid to lead trainees in the field and that he anticipated a recurrence. His history indicated chronic anxiety growing out of an insecure childhood environment, a marital problem, some compulsive behavior and emotional instability. On the surface this man appeared to have a common neurotic disturbance. However, his history revealed that he had had two other episodes of unusual behavior. On one occasion, two years before, he had an episode lasting about five minutes in which he felt dizzy and could not see, though his eyes were open. He had had another episode of momentary confusion while marching with the troops. There was no history of convulsions or episodes of unconsciousness. An electroencephalogram revealed a moderate amount of high voltage 6 per second waves and many positive spikes.

CASE 2.—A reenlisted man aged 24 one day while driving suddenly stopped the car, took out a gun and shot himself in the chest. He was referred to the consultation service after discharge from the surgical ward with the diagnosis of severe neurotic depression with a suicidal tendency. Careful inquiry revealed that he was

6. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. **50**:111-128 (Aug.) 1943.

7. Gibbs, E. L., and Gibbs, F. A.: Diagnostic and Localizing Value of Electroencephalographic Studies in Sleep, A. Research Nerv. & Ment. Dis., Proc. (1946) **26**:366, 1947.

not particularly depressed at the time of this incident. Though he remembered it, he could not understand why he had shot himself. His history revealed that he had had a few short periods for which he was amnesic. There were no convulsive phenomena, loss of consciousness or history of major emotional problems. The electroencephalogram revealed a dysrhythmic record with much psychomotor activity.

Case 3.—A Negro aged 24, a reenlistee, was referred from the station hospital because of headaches. His company reported that he had been on sick call frequently and had been court-martialed for being absent without official leave. The present illness dated back two years to a head injury in which he had received a skull fracture and had been unconscious for two weeks. Prior to this he had been happily married. He had been taking a radio technical course under the "GI Bill of Rights." Subsequently, he became nervous, began to fail in school, suffered from headaches and experienced marital difficulties. He "passed out" for short periods and had a number of fights with his wife which he was not able to recall afterward. On one occasion he threw an ax at her. On another he attempted to choke their child. After separation from his wife, seven months before the interview, he began to hear her voice calling him "bad names." At the time of the interview he told of recent auditory and visual hallucinations and exhibited paranoid ideation. The background history revealed seclusiveness and difficult social adjustment in childhood. The electroencephalogram showed a moderately dysrhythmic record compatible with interseizure epilepsy; some psychomotor features were present.

Other Cases.—The significant histories of other cases in which the electroencephalograms had psychomotor features are summarized as follows:

A man went to sleep at night and remained asleep for twenty-four to twenty-eight hours.

A man frequently walked in his sleep but had no other history suggestive of epilepsy.

A man suddenly hit a friend with a guitar, though he was not angry with him. This man also had spells in which he began to run away from people for no obvious reason. There was no amnesia for these episodes.

A man, with no history of convulsions, had on repeated occasions, when he was teased by his friends, become unconscious for fifteen minutes.

A man had spells of amnesia, during which he stole things.

A man had focal seizures in which his head and eyes turned to the right. In addition, he had other episodes in which he appeared to be conscious, but in which his mind was occupied with thoughts he could not recall afterward. He also experienced "funny" feelings in the abdomen and throat during the latter attacks.

A man had passing-out spells without convulsions and spells of irrational behavior, such as breaking dishes and overturning a table. He had amnesia for these attacks.

A man had nocturnal episodes, during one of which he struck his mother and during another of which he shouted that he was being chased by airplanes. He was amnesic for these periods. In addition, he was a frequent sleepwalker.

It is noteworthy that none of these patients had histories of convulsions, tongue biting, soiling or wetting. Only 2 had periods of unconsciousness. Some did not have amnesia, but merely could not understand why they behaved in the way they did.

A few patients had psychomotor epilepsy in conjunction with grand mal. For example, a man had generalized convulsive seizures, occurring in sleep. During some of these he would moan and call for his father and occasionally beat his head on the bed.

While psychomotor epilepsy occurs in conjunction with grand mal or petit mal attacks, we have seen many cases in which it was the only epileptic manifestation. In our series, 15 patients had histories of psychomotor epilepsy alone, whereas only 4 had both psychomotor and grand mal attacks. Moreover only 1 of 15 patients with pure psychomotor epilepsy was referred because of the possibility of epilepsy. Thus, if the old criteria for epilepsy are adhered to before the diagnosis is made, many cases of the psychomotor type will be missed. Whenever a person appears to behave irrationally and can give no reason for his behavior, psychomotor epilepsy should be suspected.

Lennox [2] stated the opinion that sodium diphenylhydantoinate (dilantin sodium®) helps about two thirds of patients with psychomotor epilepsy. He expressed the belief that phenobarbital is of little value and that trimethadione (tridione®) taken alone is ineffective in the therapy of this condition. Gibbs [1] expressed the belief that all antiepileptic substances, including phenobarbital, diphenylhydantoin sodium, trimethadione and mesantoin® (3-methyl-5-phenyl-5-ethylhydantoin), should be tried, but that medical treatment is generally unsatisfactory. However, most experts are uniformly optimistic concerning the results of therapy and believe that judicious administration of drugs results in satisfactory control of about 75 per cent of patients in this group.[4] We have used diphenylhydantoin and phenobarbital in the treatment of our patients. Our routine procedure is to give an initial dose of diphenylhydantoin sodium, 1½ grains (0.1 Gm.) three times a day, after meals, and of phenobarbital, 1½ grains, at bedtime. This represents a standard initial adult dose. The dosage is modified, if necessary, at monthly intervals to meet the requirements of the individual case. Psychotherapy, as in all forms of epilepsy, is a useful adjunct in treatment; an integral part of this is the education of the patient as to the nature of his illness. Owing to the difficulties encountered in follow-up of patients from an Army consultation service, we are not prepared to offer any conclusions as to the results of therapy in our cases.

According to present Army policy,[8] persons with paroxysmal convulsive disorders and disturbances of consciousness, including psychomotor attacks, are eligible for enlistment or induction if these attacks are controlled by medication. Nevertheless, because of the particular hazards of military life, it has been our policy to recommend most of these persons for discharge.

8. Army Regulation 40-115, Physical Standards and Physical Profiling for Enlistment and Induction, Paragraph 77 f.

SUMMARY

Psychomotor epilepsy is an important problem in an Army psychiatric consultation service from the standpoint of incidence, differential diagnosis, therapy and disposition.

During the period Jan. 1 to Feb. 28, 1949, 19 patients with psychomotor epilepsy were seen, forming 56 per cent of all patients with convulsive disorders and 2.9 per cent of the total number of patients referred.

Several cases of psychomotor epilepsy, illustrating problems of differential diagnosis, are presented.

The importance of diagnosing this condition is noted, and the possibility of response to medication (especially diphenylhydantoin [dilantin®]) is indicated.

The importance of awareness of the manifestations of psychomotor epilepsy, careful history taking and the use of the electroencephalograph in establishing the diagnosis of this condition is emphasized. The incidence of psychomotor epilepsy unassociated with grand mal or petit mal is probably higher than is generally acknowledged.

MESANTOIN® IN TREATMENT OF EPILEPSY

A Report on Two Hundred Patients Under Treatment for Periods Ranging from Two Months to Four Years

HARRY L. KOZOL, M.D.
BOSTON

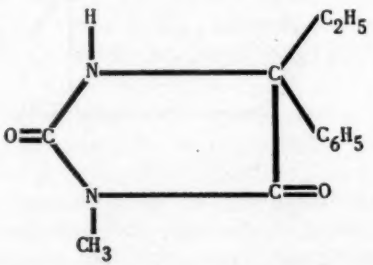
THE CORRECT evaluation of any new drug comes only through treating large numbers of patients over long periods and then carefully comparing the results with those obtained with older, proved drugs. Such evaluation includes the limitations and dangers of the new drug, as well as its advantages.

Mesantoin® (3-methyl-5,5-phenylethyl hydantoin) appears to be a valuable addition to the small list of drugs which have been proved effective in the treatment of epilepsy; in fact, I have the impression that it is the most effective antiepileptic agent generally available at this time. Many epileptic patients who had failed to respond satisfactorily to previous medication, including phenobarbital and diphenylhydantoin sodium (dilantin-sodium®), did respond remarkably to mesantoin.®

This paper is a report of my experience in treating 200 epileptic patients with mesantoin® for periods ranging from two months to four years. In this entire group, there was an average improvement of 90 per cent as judged by a reduction in the frequency of the seizures and of 75 per cent as judged by an increase in the longest interval between seizures; and even better results were obtained in certain categories of patients. Twelve and one-half per cent of the patients in this series were not helped by mesantoin.®

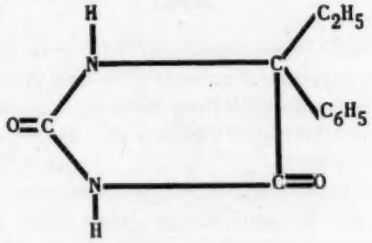
CHEMISTRY

The structural formula of mesantoin® is:



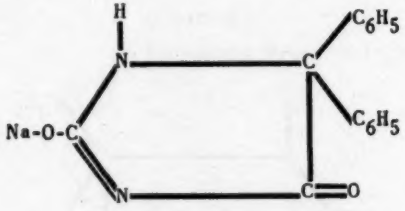
From the Neurological Unit of the Boston City Hospital, and the Department of Neurology of the Harvard Medical School.

Mesantoin® bears resemblance to both nirvanol® (phenylethylhydantoin) and dilantin® (diphenylhydantoin sodium). All three drugs are derivatives of hydantoin; and, while they have somewhat similar actions and side effects, there are also decided differences which are undoubtedly due to the differences in their structures. For years nirvanol® has been known as a drug which tends to produce an acute rash in a large proportion of patients. Its structural formula is:



Mesantoin® also tends to produce a rash, but to a much lesser degree than nirvanol.® The exact incidence is given later. On the other hand, no claims have been made for either an anticonvulsant or a sedative property of nirvanol,® whereas mesantoin® has strong anticonvulsant properties and a substantial sedative effect.

While diphenylhydantoin (dilantin®) also may produce a rash, it does so to an even lesser degree than does mesantoin,® nor does it exhibit the sedative properties of mesantoin.® On the other hand, it tends to produce motor incoordination, an effect which is rarely seen with either mesantoin® or nirvanol.® The sodium salt of diphenylhydantoin is rather stable, whereas the sodium salt of methylphenylethyl hydantoin (mesantoin®) is rather unstable. The structural formula of dilantin® is:



RESULTS

The over-all results of treatment with mesantoin® are summarized in table 1. The frequency of attacks for the entire group of 200 patients was reduced to an average of one tenth, thus resulting in an improvement of 90 per cent. For the same group of patients, the average duration of the longest intervals between attacks was quadrupled.

The entire group of 200 patients was arbitrarily subdivided into three groups, designated as "greatly improved," "improved" and "unimproved." No patient was considered as having been at all improved unless the frequency of his attacks was reduced at least one-half and/or the longest interval between attacks was at least doubled. All tabulations on the patients were started on the first day of treatment with mesantoin.® In order that the patient be listed as "greatly improved," the average frequency of his seizures had to have been reduced to at least one-fourth and/or the longest interval between attacks at least quadrupled. Sixty per cent (132) of the entire series of patients fell into this "greatly improved" group. Twenty-two per cent (43) of the patients fell into the "improved" group, and only 12 per cent (25) of the patients fell into the "unimproved" group. It should be noted that many patients in this "unimproved" group did actually show con-

TABLE 1.—*Over-All Results of Mesantoin® Therapy*

	Average Frequency of Attacks per Month			Average of Longest Interval Between Attacks (Months)		
	Before "Mesantoin"	After "Mesantoin"	Improvement, per Cent	Before "Mesantoin"	After "Mesantoin"	Improvement, per Cent
Entire series of 200 patients	15.5	1.6	90	2.5	10	75
"Greatly improved" group (132 patients)	20	0.6	97	2	13	83
"Improved" group (43 patients)	5.9	1.6	73	3.3	6	45
"Unimproved" group (25 patients)	7.7	6.9	9	3.4	4.4	23

siderable improvement but failed to meet the high qualifications for inclusion in the two "improved" groups.

In the "greatly improved" group, of 132 patients, the average frequency of attacks was reduced to one thirty-third the frequency before mesantoin® treatment and the longest interval between attacks was increased on an average of over sixfold. Thus, there was an improvement of 97 per cent in the average frequency of attacks and an improvement of 83 per cent in the average duration of the longest interval between attacks.

In the "improved" group, the average frequency of attacks was reduced to nearly one-fourth the frequency before mesantoin® treatment was instituted, thus giving an improvement of 73 per cent, and the average duration of the longest interval between attacks was nearly doubled, giving an improvement of 45 per cent. Even in the "unimproved" group the actual improvement in the average frequency of attacks amounted to 9 per cent, and the improvement in the average duration of the longest interval between attacks to 23 per cent.

These figures appear particularly significant in view of the fact that 176 of these patients (88 per cent) had antiepileptic treatment before mesantoin® was administered to them and 153 patients (76 per cent) had been treated with diphenylhydantoin sodium before receiving mesantoin.®

Each patient in the series was treated with caution, and with concern only for a reduction in his particular seizures. No special attempt was made to displace any type of therapy with mesantoin,® and in most instances in which the patient was already under treatment mesantoin® was added as a supplement, although it did ultimately displace all other drugs in the treatment of a number of patients.

In this series, 109 patients received mesantoin® alone. This number included 24 patients who had never received any treatment or were not under treatment with any other drug at the time that mesantoin® therapy was instituted, and 85 patients who were switched over entirely to mesantoin.® Ninety-one patients took mesantoin® in combination with other drugs, mainly diphenylhydantoin sodium.

Of the 200 patients in the series, 124 were male and 76 were female. Only 18 of the patients in the entire series were 12 years of age or under. Of the latter group, the average age was 8.5 years.

The duration of treatment ranged from two months to four years, with an average duration of 17.62 months. Chart 1 shows the distribution of patients according to months of treatment. It will be seen that there was included in the series 1 patient who had had only two months of treatment, 5 patients who had had only three months of treatment, 3 patients who had had only 4 months of treatment and 3 patients who had had only five months of treatment. Thus, in the entire series, only 12 patients were included who had been under treatment for less than six months. Nineteen patients had been under treatment with mesantoin® for three years or longer; 51 patients, or 25 per cent of the entire series, had been treated with mesantoin® for two years or longer. For this group the average duration of treatment with mesantoin® was 31.9 months.

The results of treatment according to the duration of treatment are as follows: In the group treated with mesantoin® for two years or longer, the average premesantoin® frequency of attacks was 8.6 per month, while the average postmesantoin® frequency was 0.3 attack per month, or an improvement of 96.5 per cent. The average longest duration between attacks before mesantoin® therapy was 2.6 months, and the average period of freedom from attacks after mesantoin® therapy was nineteen months, or an improvement of 86.32 per cent. Five patients in this group of 51 had received no treatment before mesantoin therapy; 18 had received diphenylhydantoin (dilantin®) sodium alone, and 28 had received a combination of diphenylhydantoin sodium and other drugs.

including phenobarbital in most cases. In treating these patients, 30 received mesantoin® alone, and 21 received a combination of mesantoin® and diphenylhydantoin sodium. The average duration of mesantoin® treatment for the whole group of 51 patients was thirty-two months. The results of treatment were as follows: Forty-six were included in the "greatly improved" group; 4, in the "improved" group, and 1, in the "unimproved" group.

The results appear even better in the small series of 19 patients who had been under treatment with the drug from three to four years. In

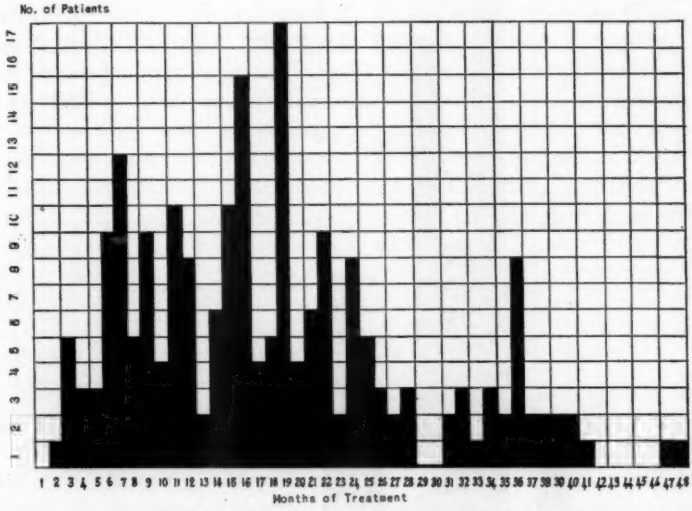


Chart 1.—Distribution of patients according to duration of treatment.

TABLE 2.—*Relation of Type of Epileptic Attack to Response to Treatment*

Type of Epileptic Attack	No. of Patients	Response to Treatment		
		"Greatly Improved"	"Improved"	"Unimproved"
Grand mal alone	143	94	36	13
Focal alone	5	3	..	2
Psychomotor alone	10	9	..	1
Akinetic alone	2	..	1	1
Myoclonic alone	1	1	..	..
Psychomotor and grand mal	17	12	1	4
Petit mal and grand mal	3	2	..	1
Akinetic and focal	1	1	..	..
Focal and grand mal	3	2	..	1
Akinetic and grand mal	1	..	1	..
Abortive and grand mal	5	5	..	..
Other combinations	9	5	2	2

this group, the average frequency of attacks before mesantoin® therapy was 10 per month and the frequency of attacks after mesantoin® therapy

was 0.1 per month, giving an average improvement of 99 per cent. The average of the longest interval between attacks before mesantoin® therapy was four months and the average of the longest interval between attacks after mesantoin® therapy was 23.31 months, a sixfold improvement. This group of 19 patients had received previous treatment as

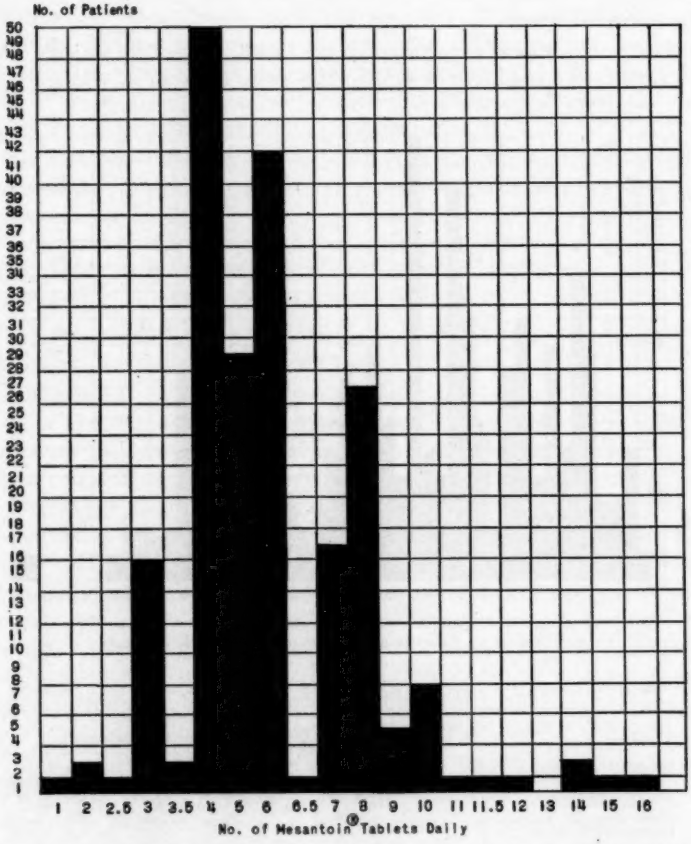


Chart 2.—Distribution of patients according to range of the dose of mesantoin.®

follows: diphenylhydantoin alone, 5 cases; diphenylhydantoin and phenobarbital or other drugs, 12 cases; no treatment, 2 cases. Fifteen of these patients took mesantoin® alone, and 4 took mesantoin® and diphenylhydantoin. One of these patients had initially taken phenobarbital in addition to the mesantoin® but was made intolerably drowsy by the combination. One of the other patients had taken mephobarbital

(mebaral®) for a period but finally discontinued it. In this group of patients, who had been under treatment with mesantoin® for three to four years, the average duration of mesantoin® treatment was 38.5 months. The relation between duration and results of treatment is demonstrated by the fact that 18 of these patients fell into the "greatly improved" group and 1 into the "improved" group. None of these patients was considered "unimproved." It is probable, of course, that no patient who did not receive some benefit before three years would have continued medication. The types of seizures suffered by the patients and the response to treatment are summarized in table 2. It will be noted that 143 of the patients had grand mal alone; 65 per cent of these patients were "greatly improved" and 25 per cent were "improved," giving a total of 90 per cent who were improved. This matches exactly the figure of 90 per cent for the 10 patients with psychomotor epilepsy. In this group there was apparently an all or none phenomenon. The 9 patients who gained benefit were considered "greatly improved." No patient was considered only "improved"; 1 patient was "unimproved." When patients with attacks of psychomotor epilepsy and those with grand mal seizures were combined in a group of 17, 70 per cent showed improvement (65 per cent were "greatly improved") and 30 per cent were "unimproved." For 5 patients who had not only frank grand mal attacks but also multiple abortive grand mal attacks, there was a 100 per cent figure for the "greatly improved" group.

The average daily dose of mesantoin® for the entire group of 200 patients was 0.583 Gm. The average daily dose for the 18 patients aged 12 years or under (average 8.5 years) was 0.39 Gm., and the average dose for the 182 other patients in the series (adolescents and adults) was 0.6 Gm. As a matter of fact, this average is purely statistical and gives a misleading impression about the use of mesantoin.® It would be better to speak of the range of the dose, because there were wide individual variations. Thus, some adults could tolerate only 0.3 or 0.4 Gm. daily or required only that much for satisfactory control of their seizures, while other adults took or required as much as 1.8 Gm. (18 tablets daily). The range of the dose is shown in chart 2.

COMMENT

Results.—The statistical presentation of the remarkable effectiveness of mesantoin® in the treatment of all forms of epilepsy other than brief absences, now recognized as petit mal, does not tell the whole story. It is of interest to note that mesantoin® appears to be more effective in controlling epilepsy secondary to cerebral trauma than does diphenylhydantoin (dilantin®) sodium, phenobarbital or any other drug. Eighteen patients gave a history and presented neurologic signs of gross cerebral

insult. Two had long-standing hydrocephalus; 3 had hemiplegia; 2 had had cerebral emboli from congenital or rheumatic heart disease; 1 had had a subarachnoid hemorrhage; 1 had had a suprasellar cyst removed; 4 had had infections (1, mastoiditis with epidural abscess; 1, brain abscess following otitis media; 1, mastoiditis with cerebrothrombophlebitis, and 1, infantile cerebrothrombophlebitis). These patients were included diagnostically in the grand mal groups if their seizures were generalized or in the special focal groups if their seizures were focal. Surgical treatment of epilepsy had been attempted for 4 patients. However, as attacks

TABLE 3.—*Response of Patients with Gross Brain Injuries to Treatment with Mesantoin®*

Patient's Initials	Rating of Result	Frequency of Attacks		Longest Free Interval, Months		Dose, Gm.	"Mesantoin" and Other Drugs
		Before "Mesantoin"	After "Mesantoin"	Before "Mesantoin"	After "Mesantoin"		
V. D.	Greatly improved	8	0.1	2	23	0.8	Alone
P. M.	Greatly improved	2	0	0.5	19	0.8	Alone
J. R.	Greatly improved	0.6	0.2	1	14	0.5	Alone
W. K.	Improved	0.6	0.3	4	6	1.0	"Dilantin"
A. G.	Greatly improved	8	0	0.7	15	1.6	Alone
W. K.	Unimproved	0.1	0	13	13	0.6	"Dilantin"
A. G.	Greatly improved	100	0	0.25	11	0.5	"Dilantin"
J. F.	Greatly improved	1	0.3	2	5	0.6	"Dilantin"
F. T.	Improved	30	15	0.25	0.5	1.2	"Dilantin"
J. B.	Greatly improved	6	0	6	11	0.5	"Dilantin"
M. K.	Greatly improved	4	1	0.7	1.5	0.8	"Dilantin"
C. B.	Greatly improved	4	1	0.5	3.5	0.4	"Dilantin"
I. B.	Greatly improved	100	1	0.06	2	0.7	Alone
E. W.	Greatly improved	1.5	0.2	0.7	5	0.4	Alone
H. D.	Improved	40	12	0.03	0.5	0.8	"Dilantin"
J. S.	Greatly improved	30	6	0.25	1	0.4	Alone
H. L.	Greatly improved	4	1	0.7	1.5	0.4	Alone
R. R.	Unimproved	0.4	0.3	7	8	1.0	Alone
Average		18.8	2.13	2.20	7.85	0.720	
		Improvement 88.67%		Improvement 71.98%			

persisted, these patients had sought further help. The results of the treatment of this group of patients with gross cerebral injury are summarized in table 3. It is important to note that most of these patients had previously been treated with diphenylhydantoin sodium in the maximal tolerable doses and had, in addition, received other anticonvulsant drugs.

From my experience with this small group of patients with gross brain injuries, it would appear that mesantoin® is the drug of choice in the treatment of epilepsy of such origin. Furthermore, it would seem advisable to give each epileptic patient with a gross cranial injury a thorough trial with mesantoin® before resorting to surgical measures.

Only 25 patients, or 12 per cent of the entire series, were considered "unimproved." In fact, as has been pointed out, a number of these patients did have some improvement. Furthermore, there was hardly a

patient in this group who did not experience some benefit from taking mesantoin.® Most of these patients had been epileptic for many years, and some had associated stunting or deterioration of mentality. One adult had attacks of akinesia. These attacks apparently differed from the akinetic attacks sometimes seen, with 3 per second waves in the electroencephalographic recordings, in that this patient did not show any 3 per second wave and spike forms.

The diagnosis in all cases in the series was based on descriptions, and in many cases on observation, of attacks. No reliance was placed on electroencephalographic recordings, which were made on almost all patients. Except for the 3 per second wave and spike form, which is often seen with "absences" in children and adolescents, no reliance can be placed on the electroencephalogram in guiding one to a clinical diagnosis of the type of attack or to desirable therapy. Many of these patients had average normal electroencephalograms. In some cases the electroencephalogram deviated more and more from the average normal as the patient grew better and better. The electroencephalogram is overrated as an instrument in the diagnosis and treatment of epilepsy, and it should be looked on as still in the experimental stage of development.

Toxicity.—No death ascribable to mesantoin® has appeared in this series of 200 patients, or in my personal experience with an even larger group. Three of the patients in the series are dead. One was killed in an automobile accident, and 1 died of acute hepatitis. While it is possible that mesantoin® may have been a factor in producing that death, a complete report of the case submitted to the editor of THE JOURNAL evoked the reply that the evidence did not seem to be sufficient to ascribe the death to mesantoin.® Nevertheless, those who use this drug would do well to be alert for the possible appearance of hepatitis. The third patient, who had attained complete freedom from seizures under treatment with a combination of mesantoin® and diphenylhydantoin sodium, stopped taking both drugs. One month later a sulfonamide ointment was applied to one arm for infectious lymphangitis, followed by oral administration of large quantities of sulfonamides. He died of acute agranulocytosis. The medical consultants were insistent that the death had been caused by the sulfonamides alone.

Aird [1] reported a death from aplastic anemia, expressing the opinion that it had resulted from the administration of mesantoin.® He pointed out, however, that the patient had not been carefully watched and that the conclusions had been constructed from the available facts. To a request on my part, he generously made further investigation of the case and elicited the interesting information that the patient had probably received sulfonamides some time before death.

1. Aird, R. B.: The Treatment of Epilepsy with Methylphenylethyl Hydantoin (Mesantoin), California Med. **68**:1-6, 1948.

Ruskin [2] reported a fatal case of fulminating dermatitis bullosa medicamentosa, due in his opinion to mesantoin.® The patient, a 10 year old girl, had a history of frequent cutaneous reactions to various drugs, including the sulfonamides and anticonvulsants. She received mesantoin, 0.3 Gm., daily for twelve days, when there developed a fatal rash with changes in the blood picture.

Frank [3] reported a case of fatal pancytopenia in a Negro boy aged 17 and recovery from severe pancytopenia in a man aged 31, the condition in both cases following the use of mesantoin.®

Further evidence demonstrating the low toxicity of mesantoin® comes from one of my cases, in which a boy aged 17, weighing approximately 150 pounds (68 Kg.), made a serious attempt at suicide by ingesting 72 tablets (7.2 Gm.). When found, approximately eight hours later, he was in a deep stupor and was admitted to a hospital. While he did not appear dangerously ill at any time and his respirations, pulse and blood pressure were within normal limits, he could not be roused for several hours. However, within twenty-four hours of the time he had taken the drug, he awakened and appeared entirely free of its effects within thirty-six hours.

Exfoliative dermatitis appeared in 2 of my patients, 1 of whom was included in the present series of 200. The first patient, a man aged 66, three months after he started mesantoin® treatment complained that he had had a rash for a year and chills and pains for a week. Examination of the blood showed 40 per cent eosinophils; this was reduced to 4 per cent in four days. The dermatologist who was called in consultation described his rash as "eczematoid—almost exfoliative." The second patient who exhibited exfoliative dermatitis was a poorly nourished man aged 60. A severe rash developed two months after the institution of mesantoin® treatment. Two weeks later studies of the blood and urine revealed an entirely normal picture. It would seem, then, that there is a likelihood of producing exfoliative dermatitis in persons past the age of 60. It should be noted that both these patients were poorly nourished; one wonders whether vitamin deficiency may not have contributed in one fashion or another.

A rash of a morbilliform or scarlatiniform type appeared in 7.7 per cent of my first series of 104 patients. Most of those patients have been absorbed into the present series of 200. It became obvious that almost every patient who had acquired a rash could be desensitized to mesantoin®

2. Ruskin, D. B.: Dermatitis Bullosa Due to Mesantoin, J. A. M. A. **137**:1031-1035 (July 17) 1948.

3. Frank, C. W., and Holland, J. F.: Pancytopenia from "Mesantoin," J. A. M. A. **138**:1148-1150 (Dec. 18) 1948.

if administration was begun over again in tiny doses. I decided therefore that I might guard against the appearance of any rash by starting mesantoin® treatment of all patients in very small initial doses. Since I have used this method of initiating the administration of mesantoin,® a rash has appeared in only 1 patient, and it seems that even that patient is being desensitized on extremely small doses. It is fair, therefore, to make the categoric statement that if administration of mesantoin® is begun in very small doses with very gradual increment there is virtually no likelihood of its producing a rash. This series contains patients who have been maintained on mesantoin® despite the fact that they had manifested rashes with diphenylhydantoin sodium and/or phenobarbital.

Mesantoin® does not produce hypertrophy of the gums or hirsutism, nor does it cause motor incoordination, ataxia or diplopia. Neither does it produce gastric distress. Numerous patients in whom gingival hypertrophy had developed with diphenylhydantoin sodium experienced a welcome recession of the hypertrophy when the drug was replaced by mesantoin.® Drowsiness is the commonest undesirable side effect of mesantoin® administration. Most patients who receive the drug experience drowsiness in the course of treatment. It is directly related to the tolerable dose for the individual patient. Some patients exhibited drowsiness with doses as small as 0.3 Gm. daily, while others were able to tolerate doses six times as large (1.8 Gm. daily) without experiencing any drowsiness. In fact, it has been my policy to use the development of drowsiness as a test for the maximal tolerable dose. Thus, I usually increase the dose in each case until drowsiness appears; then it can be reduced slightly.

Mesantoin® synergizes with both diphenylhydantoin sodium and phenobarbital. However, because its principal side effect is drowsiness, it should not be given with phenobarbital, as the soporific synergy of the two drugs is summative. Mesantoin® is much more effective than phenobarbital as an anticonvulsant. But the reason that diphenylhydantoin sodium and mesantoin® were developed was that phenobarbital was not a satisfactory anticonvulsant, owing in large part to its soporific effect. Since mesantoin® is much more effective as an anticonvulsant and nowhere near as soporific as phenobarbital, it is unwise, in my opinion, to give them together, as the addition of the phenobarbital produces drowsiness at the expense of the anticonvulsant effect. By adding phenobarbital to mesantoin,® one limits the total amount of mesantoin one can give. Loscalzo [4] presented an opposite point of view. However,

4. Loscalzo, A. E.: Treatment of Epileptic Patients with a Combination of 3-Methyl-5,5-Phenylmethyl-Hydantoin and Phenobarbital, J. Nerv. & Ment. Dis. **51**:537, 1945.

in his original paper [5] he noted that a combination of phenobarbital and mesantoin® produced drowsiness in some patients and that it was advisable to eliminate the phenobarbital for those patients. I asked Rothlin,[6] who played a part in the development of mesantoin,® why it had been offered to medical investigators in association with phenobarbital. He explained that he had received complaints that the drug produced a rash and he had a theory that phenobarbital might help in inhibiting the production of rash. After all, if phenobarbital can add anything to mesantoin,® there is no place for mesantoin® at all.

The synergy between mesantoin® and diphenylhydantoin sodium is an extremely fortunate one. Diphenylhydantoin sodium rarely, if ever, produces drowsiness, while mesantoin® rarely, if ever, produces ataxia. Thus, it is possible to administer the two drugs together without confusing their toxic effect.

There are some defects in the present series. It will be noted that it contains relatively few children. There is no doubt that experience in the administration of mesantoin® to a larger group of children would be valuable.

It should be noted that this series of cases represents a severe test of the efficacy of a new anticonvulsant, because most of the patients had been treated with maximally tolerable doses of other anticonvulsants. Thus, in a sense the series is a selected one, the selection being on the basis of recalcitrance to previous treatment. There is no reason, therefore, that results of a comparable sort cannot be obtained in the treatment of a more average series of epileptic patients.

REPORT OF CASES

CASE 1.—P. M., a woman aged 20, had had psychomotor attacks for twelve years. In the two years preceding mesantoin® treatment she averaged at least one hundred such attacks a month and frequently had as many as ten daily. In each attack she would wander about aimlessly, urinating as she walked. These attacks, which had grown worse in recent years, resulted in the withdrawal of a college scholarship. She was unable to hold any sort of job except in a 10 cent store where her sister was the manager. Doses of 0.5 and 0.6 Gm. of phenylhydantoin sodium failed to reduce the frequency of the attacks. The longest period of freedom from attacks previous to mesantoin® treatment was one month. Mesantoin® treatment was begun thirty-six months prior to the time of this report. Her attacks were reduced to a frequency of 0.05 per month, and she has not had a single attack for two years. She takes 0.9 Gm. of mesantoin® daily. She holds a steady job as a teller in a bank.

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5. Loscalzo, A. E.: The Control of Epilepsy: An Interim Report on 3-Methyl-5,5-Phenylethylhydantoin and Phenobarbital Therapy, J. A. M. A. **135**:496-500 (Oct. 25) 1947.

6. Rothlin: Personal communication to the authors.

CASE 2.—C. C., a woman aged 27, had had grand mal seizures for twenty-two years. She had an average of twelve seizures per month, and in the five years preceding mesantoin® treatment she had not been without a seizure more than three months at any one time. Mesantoin® treatment was begun thirty-seven months prior to the time of printing. In the first four months it was overlapped with the diphenylhydantoin sodium she had been taking. In the last thirty-three months she has received mesantoin® alone. She has not had a single attack for thirty-seven months.

CASE 3.—A. G., a woman aged 41, had suffered from grand mal and psychomotor epilepsy since infancy. She averaged eight seizures per month and many auras. Her longest free interval in recent years was two weeks. Mesantoin® treatment was begun sixteen months ago and the patient has remained free of attacks and auras for fifteen months. She takes a total of 1.6 Gm. of mesantoin® daily and tolerates this high dose without drowsiness. Her general health and attitudes have been immeasurably improved.

CASE 4.—H. A., a woman aged 34, had had grand mal epilepsy for nineteen years. She averaged 0.75 seizures per month, and her longest interval of freedom from attacks was nineteen months. She had been treated with bromides and with diphenylhydantoin sodium. To quote the physician who referred this patient to me, "More serious than the seizures is the slough of despond into which she has fallen and which reaches to her chin." She started treatment with mesantoin® forty-one months prior to the time of this report, and she has not had a single seizure during that time. She takes 0.4 Gm. of mesantoin® daily. This patient now works in the automatic bargin basement of a busy Boston store. She is self assured and lives a normal, happy life.

CASE 5.—F. A., a man aged 29, had had grand mal epilepsy since the age of 1 year. He averaged four attacks each month, and the longest free interval between attacks had been five months. He had been under treatment with phenobarbital and with diphenylhydantoin sodium. The patient has now been under treatment with mesantoin,® 0.4 Gm. daily, for forty months and has been free of attacks for the past thirty-eight months. The patient had been made drowsy with diphenylhydantoin but with mesantoin® therapy he is alert, bright and normal.

CASE 6.—F. G., a woman aged 45, had suffered from grand mal epilepsy for nine years. The onset of her epilepsy followed a subarachnoid hemorrhage. Her average frequency of seizures was one hundred per month, and she had not gone longer than a week without an attack. She was under treatment with both phenobarbital and diphenylhydantoin sodium. She has been under treatment with mesantoin for eleven months, and she has been free of seizures for eleven months. She takes 0.5 Gm. of mesantoin® daily and 0.2 Gm. of diphenylhydantoin sodium.

NOTE.—Since this paper was prepared, another case of poisoning by mesantoin® has been reported by Bloom, Lynch and Brick.[7]

A woman aged 34, who had suffered from grand mal and psychomotor seizures since the age of 5 years, began to take mesantoin,® 0.2 Gm., in February 1947. On Oct. 17, 1947 she increased the dose of mesantoin® on her own volition to 0.3 Gm. daily, because she had had increasingly frequent headaches and drowsiness and had had bleeding gums for a week. On October 27 she saw Dr. Brick. Hematologic studies revealed a scarcity of all elements, and biopsy of the bone marrow estab-

7. Bloom, N.; Lynch, J. P., and Brick, H.: "Mesantoin" Poisoning, J. A. M. A. **138**:498-499 (Oct. 16) 1948.

lished the diagnosis of aplastic anemia. Use of mesantoin® was immediately stopped. The patient was hospitalized on November 10 and vigorously treated with daily blood transfusions, penicillin, streptomycin and various hematinics. Twenty-four days after her admission to the hospital, her blood picture suddenly improved, and she was discharged from the hospital apparently recovered.

An unverified report of a death from aplastic anemia in a South-African patient has been brought to my attention. I am now reviewing a local case of claimed aplastic anemia with recovery which turned out to be simple pancytopenia and which may have been caused, in part at least, by sulfonamides administered by his physician for an infection of the upper respiratory tract.

Since this report was submitted for publication, 2 deaths, presumably ascribable to mesantoin,® have come to my attention. One case was that of fulminating bullous dermatitis with fatal gastrointestinal hemorrhage in a 13 year old boy who had received less than a total of 2 Gm. of mesantoin® in two weeks. The other was that of a woman aged 34 with a history of several suicidal attempts and hospitalizations for a mental disorder who had taken mesantoin® erratically and irregularly; she died of aplastic anemia. Both these cases will be fully reported in the near future.

115 Bay State Road.

NEUROLOGIC COMPLICATIONS FOLLOWING THE MANTOUX TEST

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IN THE first half of 1948 I observed 3 cases in which diagnostic Mantoux tests were followed by symptoms and signs of a lesion of the central nervous system. Local and general reactions to the Mantoux test appeared in these cases comparatively early, within six to twenty-four hours, while the neurologic illness followed within a few days in 2 cases and within several weeks in 1 case. The clinical picture corresponded in all cases to that of disseminated leukoencephalomyelitis (multiple sclerosis).

It is known that a leukoencephalomyelitic process may occur as a complication of extraneural infectious diseases and vaccinations. Observations of this kind were cited by Pette [1] to support the theory of the allergic origin of disseminated leukoencephalomyelitis.

Since I could find in the literature no data on neurologic complications of the Mantoux inoculation, my 3 cases will be recorded in some detail.

REPORT OF CASES

CASE 1.—*Second attack of multiple sclerosis (?) following the Mantoux inoculation.*

I. S., a maidservant aged 21, was admitted to the hospital on May 13, 1948. Her family history was without significance. She had measles in 1932 and diphtheria in 1934 and 1944. The second attack of diphtheria was complicated with scarlet fever, followed by otitis media on the left side. She was treated on both occasions with diphtheria antitoxin.

Nine to ten months after the episode of scarlet fever she suddenly felt a cramp in the left extremities, without loss of consciousness. She dropped the objects held in her hands, and her extremities went into flexion. This lasted one to two minutes. After the cramp she experienced stiffness in the left extremities and pain in the left leg and in the left side of the chest. Examination in the outpatient departments of the medical and ophthalmologic clinics revealed exaggeration of the deep reflexes in both lower extremities, hypesthesia of the distal parts of the extremities on the left side and saccadation of the ocular movements to the right. The ophthalmologist assumed the presence of a supranuclear lesion, and the diagno-

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1. Pette, H.: Die akut entzündlichen Erkrankungen des Nervensystems, Leipzig, Georg Thieme, 1942.

sis of an early stage of multiple sclerosis was made. Roentgenograms of the skull showed nothing significant except for a rich diploic vascularization. After thiamine treatment she was free from symptoms until the present illness.

Three weeks before her admission a Mantoux test was performed. A local area of erythema, 1.5 cm. in diameter, developed. After the inoculation she experienced general malaise, nausea and dizziness and vomited; some days later her right side felt numb, and she was giddy when turning her head. Once she had diplopia for about one hour. During the week preceding her admission her gait became increasingly unsteady.

Physical and roentgenographic examination of the internal organs revealed nothing pathologic. The blood pressure was 105 mm. of mercury systolic and 60 mm. diastolic. The erythrocyte sedimentation rate was 77 mm. in one hour. Blood studies revealed no abnormality.

Vision was 6/6 in each eye. The Horner syndrome was present on the right. Conjugate ocular movements to the right were slightly impaired. There was no nystagmus. The fundi and the visual fields were normal. There was slight paresis of the lower branch of the right facial nerve. She heard whispered sounds at a distance of 3 meters. The left tympanic membrane showed old fibrous scars, caused by perforations. Caloric examination elicited normal vestibular responses.

The right hand was weaker than the left. The Hoffmann sign was elicited on the left side. The abdominal reflexes were absent except in the upper quadrants. The muscular tonus of the right lower extremity was increased. The left foot was held in extension. The deep reflexes of both lower extremities were increased. The Babinski and Chaddock signs were present on the left; the Oppenheim sign and patellar and ankle clonus, on the right. Both the upper and the lower extremities were ataxic, especially on the left side. The gait revealed spasticity and ataxia of the limbs, the condition being more pronounced on the right. There was hypesthesia over the right half of the face and in the first and second sacral dermatomes on the right side.

Roentgenograms of the skull showed the same increase in vascularization as the films taken three years previously.

Lumbar puncture revealed a clear, colorless cerebrospinal fluid under a pressure of 80 mm. The total protein content was 24 mg. per hundred cubic centimeters. The cell content was 18 per 3 cu. mm.; the mastic curve was 000000. The Wassermann reactions of the blood and the cerebrospinal fluid were negative.

The temperature during the whole course of observation was normal, except on two occasions, when it rose above 37 C. (98.6 F.). On June 10 a multiple exudative erythema appeared on the posterior surface of the left ham and thigh. During her stay in the clinic the patient reported gradual improvement. Examination on her discharge, on July 8, 1948, revealed the same neurologic signs as those which were present on her admission, with decreased intensity, however.

Reexaminations were carried out on several occasions, the last on May 18, 1949. In the meantime her symptoms had been somewhat increased more or less periodically. Since the autumn of 1948 she had been feeling well. She had married on Dec. 18, 1948.

On May 18, 1949 the following neurologic picture was found: The palpebral fissure and the pupil were slightly narrower on the right than on the left. The labial branch of the right facial nerve was slightly weak. A general increase in muscle tonus was observed, being only slight in the right upper extremity and pronounced in the legs. The deep reflexes were exaggerated, being more pro-

nounced on the right side than on the left. The abdominal reflexes were present but exhaustible. The Babinski sign was elicited to a slight degree on the right. The gait was strongly ataxic and presented a combination of static and locomotor ataxia and Wernicke-Mann spasticity, especially in the left leg.

Summary.—In a young woman, the Mantoux test was followed within a few days by transient diplopia, signs of a lesion of the pyramidal tracts on each side, sensory disturbances and ataxia of the extremities. In the cerebrospinal fluid slight pleocytosis was found on one occasion. In view of the history of a neurologic illness four years earlier, the exacerbation of an old process is probable. As the previous neurologic illness occurred after an episode of scarlet fever, the possibility arises that this illness was complicated with thrombosis of the cerebral sinuses and that after the Mantoux inoculation "scar symptoms" appeared. The assumption of sinus thrombosis is supported by the increased vascularization of the skull, but the occurrence of the first neurologic attack several months after the scarlet fever, and without fulminating signs, does not favor this assumption.

The positive reaction to the Mantoux test makes it evident that the patient had had a previous tuberculous infection. For this reason, one must consider the possibility that the first neurologic illness was due to a tuberculous process of the central nervous system, which, after healing, was activated by the Mantoux test. That multiple tuberculomas may produce a clinical picture similar to that observed in this case is demonstrated by a case reported by Foix, Thévenard and Nicolesco and Gradinesco,[2] in which necropsy revealed tuberculomas in the frontal and paracentral regions. However, the normal temperature, the low erythrocyte sedimentation rate and the absence of signs of an active tuberculous process of the lungs do not support the assumption of a tuberculous process in the central nervous system in our case.

The most likely explanation is that the invading antigen elicited an antibody reaction and in this way reactivated a multiple sclerosis, of which the first attack preceded this, the second one, by four years.

CASE 2.—*Syndrome of pontile encephalitis following Mantoux inoculation.*

J. V., a housewife aged 46, was admitted to the hospital on June 1, 1948. Her family history was without significance. At the age of 6 years she had scarlet fever and diphtheria. At the age of 25, after otitis media, she had a mastoid antrotomy. At the age of 37 she was treated in a tuberculosis sanatorium; at this time she had labyrinthitis. In the same year she had pyelitis. She had had eczema on several occasions.

At the beginning of December 1947 she had a Mantoux inoculation. A local area of erythema, about 4 cm. in diameter, developed. A few days later, in the center of this area a small vesicle appeared, which later suppurated. On her

2. Nicolesco, J., and Gradinesco, O.: Syndromes pyramidalo-cérébelleuse consécutifs de la région cérébrale paracentro-frontale, Soc. de méd. hôp. Bucurest, 1942, no. 5-6.

admission a livid discoloration still marked this area. After the inoculation she experienced general malaise for several days. During the last days of December she began to have headaches. Jn January 1948 she was treated for pleuritis sicca, which healed in a few days. She had had frequent nausea and vomiting. Since the onset of the headaches she had noted reduction in vision. With her head in certain positions she had diplopia. On looking to the left she felt giddy. A few days before admission she noted numbness of the skin over her right wrist. Her gait has been unsteady since the winter of 1947, chiefly in the dark.

Physical and roentgenographic examinations of the internal organs revealed nothing pathologic. The temperature never rose above 37 C. The blood pressure was 130 mm. of mercury systolic and 70 mm. diastolic. Blood studies showed 4,500,000 red cells, 8,200 white cells and a hemoglobin concentration of 75 per cent. The erythrocyte sedimentation rate was 15 mm. in the first hour. Myopia and astigmatism were present on the left. The reactions of the pupils were normal. The eyeballs showed a slight tendency to spastic convergence on her looking forward. The ocular movements were normal to the right but were slightly impaired to the left, especially those of the left eyeball. There was horizontal nystagmus to the right. The upward movement of the eyes was possible only after elimination of binocular vision. The fundi and the visual fields were normal. There was slight facial paresis on the right side.

Motility, muscular power and tonus of the extremities were normal. The deep reflexes were livelier in the left upper extremity than in the right. The patellar reflexes were lively. There were no pathologic reflexes or sensory disturbances. Ataxia was present in both upper extremities, being more pronounced in the left. In the Romberg position the patient fell to the left.

On lumbar puncture, on June 8, the initial pressure was 120 mm., the passage was free and the fluid was clear and colorless. Its cell content was 2 cells per 3 cu. mm.; the Pandy reaction was positive, and the Nonne-Apelt reaction was negative. The mastic reaction was 000000. The Wassermann reaction of the blood was negative, and that of the cerebrospinal fluid was questionable. After the lumbar puncture the headache ceased.

The patient was discharged on June 13. At that time slight paresis of the left extremities was present. There were ataxia and adiadokokinesis on the left.

No catamnestic data were available in this case.

Summary.—In this case the complaints—headache, dizziness and numbness over the right wrist—began several weeks after the reaction to the Mantoux test. The signs of a lesion of the cranial nerves—impairment of the conjugated ocular movements with nystagmus—the reflex anomalies, paresis and ataxia, found six months later, can be explained by the assumption of a lesion at the mesencephalic and pontile levels of the brain stem. The clinical picture revealed thus a great similarity to the type of disseminated encephalomyelitis described by Redlich [3] under the name "encephalitis pontis et cerebelli."

Since the patient had been treated several years before for a pulmonary infection, it is possible that a latent tuberculous process of the central nervous system was activated by the Mantoux test. The other

3. Redlich, E.: Ueber Encephalitis pontis et cerebelli, Ztschr. f. d. ges. Neurol. u. Psychiat. **37**:1, 1917.

possibility is an activation of multiple sclerosis. The pons represents one of the predilective sites of both processes, and in 1 of Redlich's [3] cited cases necropsy proved that neurologic disorders were due to multiple sclerosis (Pette [1]).

CASE 3.—*Multiple sclerosis (disseminated leukoencephalomyelitis) following the Mantoux test.*

A. V., a clerk aged 23, married, was admitted on May 7, 1948. The family history showed nothing significant. He had had diphtheria in childhood.

On April 7, 1948 a Mantoux test was performed. A small round area of erythema developed. Several days after the inoculation he experienced general malaise and weakness of the right lower extremity and numbness of the right leg after walking for a short time. There was severe pain in the bones of the right lower extremity.

No pathologic change in the internal organs was detected. The blood pressure was 120 mm. of mercury sytolic and 80 mm diastolic. Blood studies showed 4,200,000 red cells, 9,200 white cells and 82 per cent hemoglobin. The temperature during the entire period of observation was below 37 C.

On the patient's looking to either side, a horizontal nystagmus in the direction of gaze, with a rotatory component, was observed.

The lower extremities were slightly hypotonic, but their muscular power was normal. The deep reflexes were exaggerated. The abdominal reflexes were absent. Babinski, Oppenheim and Chaddock signs were elicited on both sides. The gait was spastiataxic. The patient was unable to recognize numbers written on his skin below the seventh thoracic dermatome and he made errors concerning the position of his toes; except for that sensibility was not disturbed.

Ophthalmologic examination revealed myopic astigmatism and ectopia papillae on both sides.

Caloric tests revealed nystagmus of 120 to 130 per second on both sides; severe vomiting followed the test.

Lumbar puncture, on June 12, revealed a pressure of 170 mm. with no sign of spinal fluid block. There were 27 lymphocytes per 3 cu. mm. of fluid. The total protein content was 24 mg. per cubic centimeter. The mastic reaction was negative. The Wassermann reactions of the blood and the cerebrospinal fluid were negative.

He was treated with vitamins and arsenic and iron preparations and was discharged on June 5, 1948, with the neurologic status essentially unchanged.

The second time the patient was observed from June 25 to July 16, 1948. He felt subjectively much better. The organic symptoms were all present but had lost much of their intensity.

On reexamination on May 11, 1949, he reported fluctuations in his condition. Neurologic studies showed a rotary nystagmus to the left on his gazing to the left; a slight Wernicke-Mann predilection paresis of the lower extremities, with marked spastic reflexes, signs of pyramidal involvement, changing spasticity and hypotonia, and a slight disturbance of the deep sensibility, of the right leg. The gait indicated pronounced paresis combined with cerebellar ataxia. The caloric reactions of the vestibular system were slightly exaggerated.

Summary.—In this case, general malaise and weakness of the right lower extremity were noted several days after a Mantoux test. One month after the inoculation spastic paraparesis of the lower extremities,

absence of the abdominal reflexes and slight disturbance of the deep sensibility were found.

The signs of multiplicity of the lesion, the absence of the characteristic signs of compression in the cerebrospinal fluid and, last but not least, the remissions during the evolution of the illness exclude the possibility of spinal compression. The diagnosis of multiple sclerosis seems assured. In the absence of relevant anamnestic data, only the positivity of the reaction to Mantoux inoculation indicated a previous tuberculous infection. The other important feature of the case is the absence of any symptoms indicating a neurologic disorder at any time before the performance of the Mantoux test.

COMMENT

The question arises whether a connection between the Mantoux test and the neurologic process can be assumed. The appearance of the neurologic signs and symptoms within a short interval after the inoculation makes a causal connection at least probable. The clinical picture in each case corresponded to that of disseminated leukoencephalomyelitis. Disseminated leukoencephalomyelitis can be produced in rabbits and in other animals by extraneural injection of a mixture of brain emulsion (homologous antigen) and killed tubercle bacilli and adjuvants (Morrison,[4] Ferraro and Cazzulo[5]).

Thus, an effect of the tuberculin and tuberculotoxin on the nervous system, especially on the white substance and the meninges, seems to be established. It is probable that the patients were hypersensitive to the tuberculin in the Mantoux test. Adsorption of the tuberculin by the cells both in vivo and in vitro was proved by Holst.[6] According to Peyrer,[7] the quantity and the duration of the accumulation of the tuberculin in the tissues differs in hypersensitive and in insensitive patients. The tuberculin is present in the blood of an insensitive person for a long time, whereas in the sensitive person it disappears soon from the blood and is accumulated in the cells. It is possible that in the present cases the tuberculin injected in the course of the Mantoux test was

4. Morrison, L. R.: Disseminated Encephalomyelitis Experimentally Produced by the Use of Homologous Antigen, Arch. Neurol. & Psychiat. **58**:391 (Oct.) 1947.

5. Ferraro, A., and Cazzulo, C. L.: Production of Chronic Allergic Encephalomyelitis in Guinea Pigs by the Intraperitoneal Route, J. Neuropath. & Exper. Neurol. **8**:70, 1949.

6. Holst, P. M.: Studies on the Effect on Tuberculin, Tubercle **3**:249, 1922.

7. Peyrer, K.: Ueber das Verhalten des Tuberkulins im Organismus, Ztschr. f. Kinderh. **35**:202, 1923.

affixed to neural elements containing antibodies arising from a previous tuberculous infection, and that the subsequent antigen-antibody reaction resulted in an allergic inflammation, i. e., leukoencephalomyelitis.

The relation between multiple sclerosis and disseminated encephalomyelitis has been discussed often during the last twenty years. There are two opposing views, one of which denies their pathologic unity (Spielmeyer,[8] Hassin,[9] Hallervorden[10]) and the other, based on the common pathoanatomic characteristics (focal appearance, demyelination), assumes that they represent an essentially identical entity (Pette,[1] Környey[11]). According to the second view, the variation in the course of development of the process is the source of the differences which reveal themselves in the pathologic features and in the clinical picture of leukoencephalomyelitis and multiple sclerosis. The acute form fell under the head of disseminated leukoencephalomyelitis, while the chronic recidivant forms belong to the group of multiple sclerosis.

The possibility of a relation between multiple sclerosis and tuberculosis has also been discussed. About 1930 Löwenstein[12] reported the recovery of tubercle bacilli from the blood of patients with multiple sclerosis in a relatively high percentage. Ahringsmann[13] attempted to support the view that multiple sclerosis is a metatuberculous disease, in the same sense as tabes and dementia paralytica represent a metasyphilis of the central nervous system. However, control examinations by Friedmann, Katz and Rabinowitsch[14] did not corroborate the results of Löwenstein.

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8. Spielmeyer, W.: Infection und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1930.

9. Hassin, G.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:589 (Aug.) 1923; Neuroptic Myelitis Versus Multiple Sclerosis, ibid. **37**:1083 (Nov.) 1937; Disseminated Encephalomyelitis Versus Sclerosis Multiplex, ibid. **40**:1111 (Dec.) 1938.

10. Hallervorden, J.: Die zentralen Entmarkungskrankheiten, Deutsche Ztschr. f. Nervenh. **150**:200, 1940.

11. Környey, S.: Ueber "zentrale" Leukomyelitiden, Deutsche Ztschr. f. Nervenh. **138**:105, 1935; Myelitis, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 509; Akute, nichtspezifische, nichteitrige, entzündliche Krankheiten des Gehirns und Rückenmarks beim Menschen, Ergebn. d. Path. **36**:96, 1943.

12. Löwenstein, E.: Tuberkelbacillämie bei Erkrankungen des Zentralnervensystems, München. med. Wchnschr. **1**:1080, 1938.

13. Ahringsmann, H.: Zur Frage der Aetiologie der multiplen Sclerose, München. med Wchnschr. **1**:191, 1933; Das Problem multiple Sclerose, ibid. **2**:1938, 1931.

14. Friedmann, A.; Katz, and Rabinowitsch, L.: Untersuchungen zur Auffassung der multiplen Sclerose als Metatuberculose, Zentralbl. f. Neurol. & Psychiat. **64**:260, 1932.

Our observations prove that the Mantoux test may be followed by reactions of the central nervous system. In 1 of the reported cases the inoculation seems to have activated a preexisting neurologic lesion. Therefore, prior to performance of the Mantoux or similar tests the history taking and examination must be extended to a search for neurologic symptoms and signs, and persons suspected of having, or of having had, neurologic disease must be excluded from tuberculin tests. In the 2 other cases, however, the complications were the first manifestations of a neurologic disease. Therefore even such precautions cannot exclude the possibility of neurologic complications, though in some cases a careful neurologic examination may reveal signs of a forme fruste of multiple sclerosis, such as nystagmus and absence of the abdominal reflexes.

SUMMARY

Three cases of neurologic complications following the Mantoux test are reported. In all 3 cases the diagnosis of disseminated leukoencephalomyelitis was made. The syndrome observed in case 2 showed a great similarity to the leukoencephalomyeltis described by Redlich under the name "encephalitis pontis et cerebelli." In case 1 a previous leukoencephalitic process seemed to have been activated by the Mantoux test; in case 3 the neurologic symptoms and signs followed the test in a formerly entirely healthy person. These complications of the Mantoux test are explained as a manifestation of a neuroallergic reaction. Before performance of the tuberculin test it seems advisable to make a neurologic examination in order to exclude the presence of even slight and nondisturbing signs of neurologic disorders, which may be a basis of complications.

POLIOMYELITIS

III. Bulbar Poliomyelitis; A Study of Medullary Function

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IN SPITE of an extensive literature on poliomyelitis, few publications have been devoted to a study of the medulla oblongata by either clinical or laboratory investigators. Most of the literature deals with the clinical and histologic alterations resulting from involvement of the spinal cord. This form of poliomyelitis, however, is rarely fatal and does not present the acute problems that so often accompany the bulbar form of this disease. Probably one reason for the neglect of this problem has been the belief that the incidence of bulbar poliomyelitis is low, the 6 per cent figure of Wickman [1] still being relied on by many authorities. Generally, figures on the frequency of bulbar poliomyelitis are not entirely accurate, since many cases of mild sporadic outbreaks of this form of the disease are not reported. For example, Walsh [2] in 1925 reported 55 cases with an incidence of bulbar involvement of 58 per cent. McEachern [3] studied 6 cases, all of which were of the bulbar type. The frequency of this form of the disease is most variable from one outbreak to another. In the large epidemic in Minnesota in 1946 the incidence of bulbar involvement among unselected cases of the disease in patients admitted to the University Hospital was 23 per cent for children under 16 years of age and 32 per cent for patients beyond this age. During this outbreak 183 patients with bulbar poliomyelitis were studied and cared for at the University Hospital in a four month period. During the same outbreak the complete nervous

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This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

1. Wickman, I.: Acute Poliomyelitis (Heine-Medin Disease), translated by W. J. M. A. Maloney, Nervous and Mental Disease Monograph 16, New York, Nervous and Mental Disease Publishing Company, 1913.

2. Walsh, F. B.: A Brief Review of Forty-Five Cases of Anterior Poliomyelitis, Canad. M. A. J. **15**:482, 1925.

3. McEachern, J.: Epidemic Bulbar Poliomyelitis: Report of Six Cases with One Necropsy, J. A. M. A. **86**:90 (Jan. 9) 1926.

systems of 80 patients who died were obtained for study. Such an abundance of clinical and pathologic material has enabled us to survey in detail the symptomatology as related to special functional disturbances observed during life and to compare these clinical observations with the pathologic changes observed post mortem. Our studies indicate that bulbar poliomyelitis is not a single homogeneous entity. There appear to be at least three bulbar symptom complexes, each resulting from involvement of a specific region of the medulla and producing special functional disturbances. The most frequently recognized form consists of involvement of the nuclei of the motor cranial nerves. However, the autonomic centers within the medulla may also be injured independently or in conjunction with the cranial nerve nuclei, resulting in respiratory or circulatory failure. Scattered references are available on both the clinical and the pathologic disturbances in bulbar poliomyelitis, but no detailed reports have been published based on a large series of cases in which the many variations and individual patterns of disturbances might be detected.

Strümpell [4] in 1884 first mentioned polioencephalitis and stated that it was a form of bulbar poliomyelitis. Wickman [5] in 1905 studied 1,031 cases in Sweden and first emphasized the involvement of the brain stem, which occurred in 34 cases. Although this investigator observed specific inflammatory changes within the reticular substance, he failed to recognize their possible significance and emphasized only the alterations within the motor nuclei of the cranial nerves. Harbitz and Scheel [6] in 1907 again emphasized the localization of the pathologic process in poliomyelitis to the tegmental portion of the brain stem.

In all the earlier studies (Médin,[7] Caverly,[8] Geirsvold,[9] Perkins and Dudgeon,[10] Pasteur [11]) the authors were particularly interested in

4. Strümpell, A.: Ueber die acute Encephalitis der Kinder (Polioencephalitis acuta, cerebrale Kinderlähmung), Allg. Wien. med. Ztg. **29**:612, 1884.

5. Wickman, I.: Studien über Poliomyelitis acuta: Zugleich ein Beitrag zur Kenntnis der Myelitis acuta, Berlin, S. Karger, 1905; Arb. a. d. path. Inst. d. Univ. Helsingfors **1**:109, 1905.

6. Harbitz, F., and Scheel, O.: Akute Poliomyelitis und verwandte Krankheiten: Pathologisch-anatomische Untersuchungen aus den Epidemien in Norwegen, 1903-1906, Deutsche med. Wchnschr. **33**:1992, 1907.

7. Médin, O.: Om den infantila paralysien, med särskild hänsyn till des akuta stadium, Nord. med. Ark. **6**:1, 1896.

8. Caverly, C. S.: History of an Epidemic of Acute Nervous Disease of Unusual Type, M. Rec. **46**:673, 1894.

9. Geirsvold, M.: Epidemisk "Poliomyelit"; bakteriologiske undersoegelser, Norsk. mag. f. lægevidensk. **3**:1280, 1905.

10. Perkins, J. J., and Dudgeon, L. S.: A Case of Acute Poliomyelitis in an Adult, with Marked Bulbar and Ocular Symptoms: Microscopical Report, Brain **30**:110, 1907.

11. Pasteur, W.: Infantile Paralysis Limited to the Bulbar Nuclei, with Permanent Paralysis of Half the Face and Tongue, Lancet **2**:858, 1887.

the involvement of the cranial nerve nuclei, since the clinical picture in such a disturbance was readily recognized. Patients with this form of the disease presented evidence of paralysis of the motor cranial nerves with the production of ophthalmoplegias, facial paralyses, and so on. The most characteristic and dramatic involvement was due to disturbances in the tenth cranial nerve. The patients exhibited difficulty in swallowing and talking. There was often pooling of secretions in the throat, with resulting asphyxia. Perkins and Dudgeon [10] described specific damage to the nucleus ambiguus in a case of this type. Similar changes within the nucleus ambiguus have been described by Kino,[12] Magni,[13] Luhan [14] and Howe and Bodian.[15] Luhan, in a series of 13 fatal cases, observed changes within the motor nucleus of the tenth cranial nerve in every case although in some the cellular destruction was only moderate. Kino also concluded that the motor cranial nerves were chiefly involved in this disease.

Although implication of the motor cranial nerves, with its characteristic symptomatology, comprises the most frequent clinicopathologic picture seen, it was recognized early that other functional areas of the medulla may be involved. As early as 1908 Acuña [16] described inflammatory lesions involving the medial reticular substance of the medulla in 3 fatal cases of bulbar poliomyelitis. The significance of these lesions was not commented on by the author. Petrén and Ehrenberg [17] in 1909 first suggested that the respiratory center might be involved in this disease and described 2 cases to illustrate such involvement. Wickman [5] also suggested the possibility of respiratory disturbances resulting from bulbar involvement. Magni [13] specifically divided the clinical symptoms of bulbar poliomyelitis into two groups. Most frequently the changes implicated the cranial nerve nuclei, while less commonly the lesions injured the reticular substance, with resulting respiratory or circulatory symptoms. Since these studies of Magni, a number of authors have recognized and briefly differentiated the respiratory

12. Kino, F.: Die Poliomyelitis des Hirnstammes. (Zur Lehre von der Pathoklise), Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:332, 1928.

13. Magni, L.: Intorno al tipo bulbo-protuberanziale della malattia di Heine-Médin. (Note cliniche e anatomo-pathologiche), Riv. clin. pedia. **23**:101, 1925.

14. Luhan, J. A.: Epidemic Poliomyelitis, Arch. Path. **42**:245 (Sept.) 1946.

15. Howe, H. A., and Bodian, D.: Neural Mechanisms in Poliomyelitis, New York, The Commonwealth Fund, 1942.

16. Acuña, M.: Cas de polioencéphalomyélite aiguë chez un garçon de trois ans, avec étude anatomopathologique des centres nerveux, Arch. de méd. d. enf. **11**:405, 1908.

17. Petrén, K., and Ehrenberg, L.: Etudes cliniques sur la poliomyélite aiguë, Nouv. inconog. de la Salpêtrière **22**:273, 1909.

symptoms from those of involvement of the cranial nerves. (Petrén and Sjövall[18]; Manicatide, Bratesco and Rusescu,[19] and Brahdy and Lenarsky.[20])

It is now generally agreed that the lesions resulting in respiratory symptoms are probably situated in the reticular formation. Acuña[16] and Russel[21] described such inflammatory lesions in the reticular formation of the medulla. Thomas and Lhermitte[22] and Lhermitte and his co-workers[23] described a diffuse inflammation in the lateral portion of the retro-olivary region in cases of bulbar poliomyelitis with respiratory symptoms. Guizetti[24] described 2 cases of bulbar poliomyelitis of the respiratory type. He observed severe damage in the reticular substance extending from the lower portion of the medulla, at the level of the decussations, to the midbrain. The involvement was extensive and implicated both the medial and the lateral cell groups. No attempt was made to correlate these observations with the clinical symptoms. Wesselhoeft[25] clearly differentiated the type of bulbar poliomyelitis involving the cranial nerves from the type involving the respiratory center. He stated the belief that the respiratory center was situated under the floor of the fourth ventricle. Bodian[26] observed lesions in the reticular formation in all cases of fatal poliomyelitis.

Although a respiratory type of bulbar poliomyelitis has been recognized for many years, one finds much less attention being paid to the significance of circulatory symptoms in this disease. Magni[13] first intimated that circulatory symptoms may indicate the presence of bulbar poliomyelitis. Petrén and Sjövall[18] observed irregularities in pulse and questioned the possibility of involvement of the circulatory center in the medulla. Nordmann and Müller[27] observed a case in which there

18. Petrén, K., and Sjövall, E.: Eine Studie über die tödliche akute Form der Poliomyelitis, Acta med. Scandinav. **64**:260, 1926.

19. Manicatide, M.; Bratesco, A., and Rusescu, A.: Les troubles respiratoires au cours de poliomyélite en Roumanie, Compt. rend. Soc. de biol. **99**:1362, 1928.

20. Brahdy, M. B., and Lenarsky, M.: Respiratory Failure in Acute Epidemic Poliomyelitis: Late Results and Complications, J. Pediat. **8**:420, 1936.

21. Russel, C. K.: A Contribution to the Study of Acute Poliomyelitis Based on the Observation of Thirty-Eight Recent Cases with Two Autopsies, Montreal M. J. **39**:457, 1910.

22. Thomas, A., and Lhermitte, J.: Les lésions cérébrales et médullaires de la poliomyélite aiguë de l'adult, Rev. neurol. **1**:1242, 1929.

23. Lhermitte, J.; Pagniez, P., and Plichet, A.: Forme respiratoire ou asphyxique de la maladie de Heine-Médin, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:76, 1932.

24. Guizetti, H. U.: Betrachtungen zur Poliomyelitis des Hirnstamms, Deutsche Ztschr. f. Nervenh. **131**:29, 1933.

25. Wesselhoeft, C.: Medical Progress: Respiratory Failure in Acute Poliomyelitis, New England J. Med. **228**:225, 1943.

26. Bodian, D.: Poliomyelitis, J. A. M. A. **134**:1148 (Aug. 2) 1947.

27. Nordmann, J., and Müller, A.: Ueber die Lage eines Blutdruckregulierenden Zentrums in der Medulla Oblongata, Klin. Wchnschr. **33**:1371, 1932.

was a terminal rise of blood pressure. Autopsy revealed a lesion in the reticular substance from the level of the nuclei of the seventh cranial nerve to that of the nuclei of the glossopharyngeal nerve. The authors speculated on the possibility of a blood pressure–regulatory center in the medulla. Smith and Fineberg [28] described a vasomotor type of bulbar poliomyelitis. Clinically the patients showed rapid, thready pulse; low tension; cold, clammy, cyanotic skin; rising temperature, and falling blood pressure. This type of involvement was invariably fatal.

In spite of the scattered reports on bulbar poliomyelitis, no attempt has yet been made to study in detail the various pathologic lesions in this illness as compared and correlated with the clinical symptoms.

PRESENT INVESTIGATION

It was felt that a careful survey of our material might well contribute to a better understanding of the symptoms of this disease and might augment present knowledge of bulbar physiology. For this study the complete medulla was available in 80 cases of bulbar poliomyelitis. Serial studies were made through the entire medulla. All sections were prepared with the Nissl stain, the hematoxylin-eosin stain and Weil's stain. It was found that these three methods were adequate to permit a study of the changes occurring in the medulla. In all cases the sections were magnified on an Edinger projector and the lesions located and outlined so as better to enable visualization of their exact distribution. In a few selected cases, particularly with involvement of the autonomic nervous system, the entire medulla was reconstructed so as to determine the extent and location of the pathologic lesions. In all cases the pathologic alterations in the medulla were correlated with the clinical history of the disease. We feel from our studies that it is possible not only to divide bulbar poliomyelitis into distinct clinicopathologic entities, but to isolate and describe the location of the medullary centers regulating respiration and circulation in man.

In surveying our material, it became apparent that in bulbar poliomyelitis three types of histopathologic lesions occur: (1) a diffuse interstitial cell reaction, (2) neuronal damage (fig. 1 *A*) and (3) focal destruction of tissue (fig. 1 *B*). The diffuse interstitial involvement, although striking, appears to have little clinical correlation except in cases in which it is severe enough to cause actual destruction of adjacent nerve cells. The neuronal involvement constitutes the most important alteration because of the associated functional impairment. It is these changes that offer the best opportunity for attempted clinical correlation. Generally both these changes are observed in varying degrees in

28. Smith, E., and Fineberg, H. I.: Bulbar Poliomyelitis and Its Treatment, J. Pediat. **4**:590, 1934.

most cases of bulbar poliomyelitis. The focal necrosis probably comprises the most striking pathologic observation. These changes are present only in selected cases and, because of their complete destruction of the involved nerve cells, offer the best basis for clinical-pathologic correlation. It is on the basis of cases of focal tissue destruction that it has been possible to determine the function of specific cell groups within the medulla.

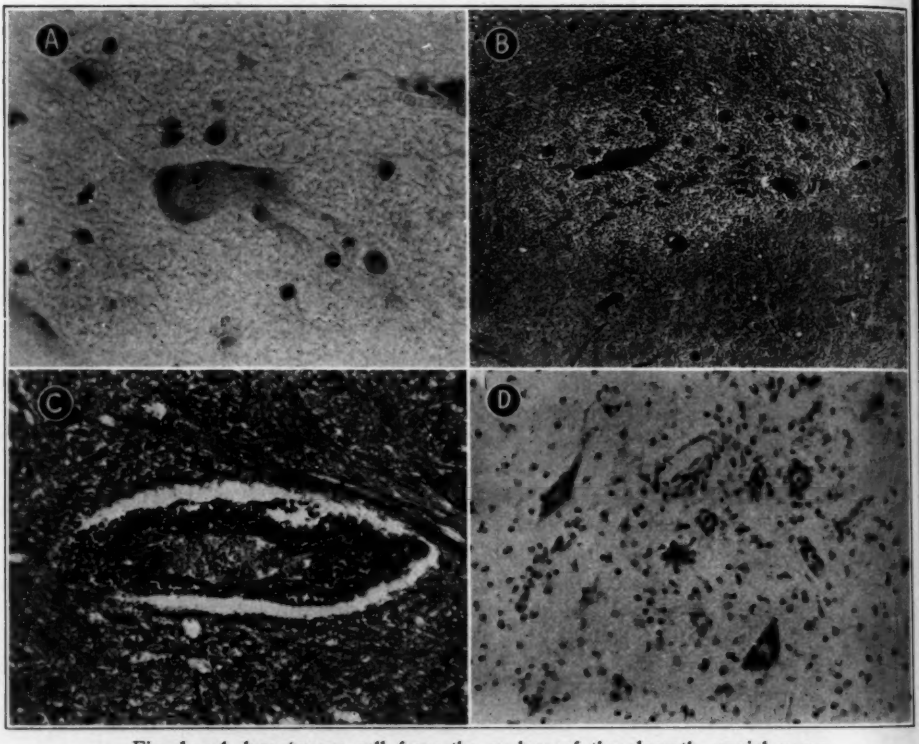

Fig. 1.—*A*, large nerve cell from the nucleus of the eleventh cranial nerve. The neuron is extremely swollen and chromatolytic. Nissl stain. *B*, section from the lateral reticular formation of the medulla. The circumscribed area of inflammatory necrosis is filled with many distended vessels. Hematoxylin-eosin stain. *C*, focal area of inflammation. The heavy layers of leukocytes are localized to the perivascular space, with only mild involvement of the adjacent tissues. Hematoxylin-eosin stain. *D*, diffuse inflammatory reaction throughout the nucleus of the twelfth cranial nerve. The nerve cells, however, are structurally intact. There was no clinical evidence of damage to the nerve cells. Nissl stain.

Although these three types of pathologic lesions may occur simultaneously, it is more convenient to discuss them separately, since their predominance plays an important role in the clinical symptoms observed in the patient.

DIFFUSE INTERSTITIAL CELL INVOLVEMENT OF THE MEDULLA

Diffuse involvement of the dorsal portion of the medulla was the predominant feature in 61.5 per cent of our cases and comprised the most frequent type of lesion seen in this disease. The detailed histologic nature of the lesions in the medulla does not differ from that of lesions in the spinal cord and has been thoroughly discussed in the literature.

These lesions consisted primarily of a mesodermal-glial (interstitial) reaction together with severe neuronal damage. In some cases the former predominated, and in others the neuronal damage comprised a most important part of the pathologic picture. The mesodermal-glial reaction consisted of focal and diffuse inflammatory elements, which varied from a few scattered cells, which incompletely surrounded a vessel, to heavy layers of leukocytes, which filled the perivascular spaces and even extended into the adjacent tissues (fig. 1 *C*). In severe cases hardly a single area within the medulla failed to reveal some perivascular infiltration.

When the perivascular infiltration was very severe, the leukocytes might extend inward to involve the vessel wall or outward to invade the adjacent tissues. Extension of leukocytes from the vessels into the adjacent tissues occurred only in cases of the severer forms. At the onset this infiltration was extremely focal, surrounding the vessel and consisting chiefly of a mixture of polymorphonuclear leukocytes. In many cases the leukocytic invasion remained localized, although varying greatly in size. Within the larger foci the underlying tissues underwent softening and fragmentation, eventually being invaded by phagocytes, which intermingled with the leukocytes already present.

In most cases one observed, in addition to these focal and perivascular collections, a diffuse leukocytic infiltration which involved to a varying degree a good share of the dorsal portion of the medulla. Macroglial reaction was never pronounced, regardless of the nature or extent of the associated interstitial reactions. This was probably due to the fact that in cases of bulbar poliomyelitis death results before such a reaction can take place.

Bleeding occurred only in cases of the most fulminating type. Hemorrhages might be either focal or diffuse and were most frequently observed in the floor of the fourth ventricle.

Although the detailed histologic nature of this interstitial reaction has received a great deal of study, much less interest has been shown in the distribution of these lesions within the medulla. In the upper portion of the medulla the inflammatory process invariably implicated certain specific regions of the dorsal part of the medulla. This region consistently extends from the floor of the fourth ventricle to the inferior olivary nucleus. It was bounded medially by the medial lemniscus and laterally by the restiform body and the descending root of the fifth cranial nerve except for a point between the latter and the olive, where the involvement extended finger-like to the surface of the medulla

(fig. 2 *a*). The involvement generally was not uniform within this area, but seemed to show a definite pattern, being less intense as one progressed dorsally. In the floor of the fourth ventricle, around the nuclei of the twelfth, tenth and eighth cranial nerves, the interstitial reaction

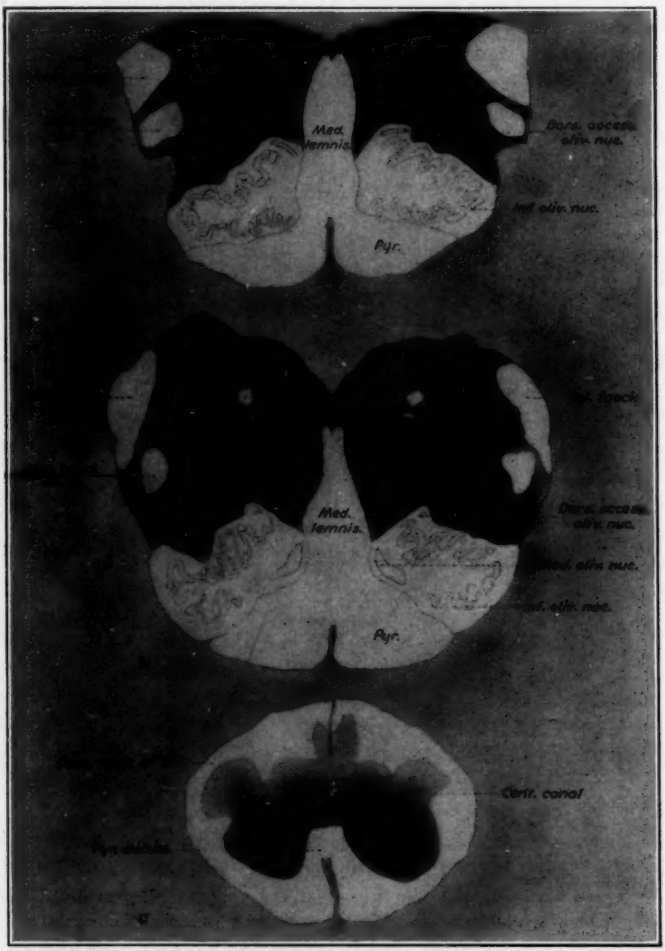

Fig. 2.—Intensity of the inflammatory reaction within the various regions and levels of the medulla, as demonstrated by the comparative darkness of the shaded areas. (*a*) Upper portion of the medulla, showing the most intense reaction in the ventral third of this region. The restiform body, the descending tract of the fifth cranial nerve and the inferior olivary nuclei are completely spared. (*b*) Middle portion of the medulla. The general distribution of the lesions is similar to that at the higher levels, although much less severe. (*c*) Lower portion of the medulla. The inflammatory process is localized ventral to the decussations, in the region of the nucleus of the eleventh cranial nerve.

was not very severe and consisted primarily of perivascular infiltrates and petechiae. In the ventral third of this region the inflammatory process was severest and consisted of extensive focal and diffuse leukocytic infiltrates. The inflammatory process in this region frequently involved and completely destroyed the nucleus ambiguus, probably producing the obstructive symptoms that caused death. It was in this region that one observed frequent and severe softening and destruction of the underlying tissues, producing areas of early inflammatory necrosis. Although inflammatory lesions were observed bilaterally, they were not always of equal severity, even though they followed the same pattern (fig. 2 *a*).

Certain structures in the upper portion of the medulla were almost never involved, a selectivity suggesting great specificity for the virus. Generally such structures were the long conduction pathways, such as the pyramidal tract, the medial lemniscus, the descending root of the fifth cranial nerve and the restiform body. The inferior olivary nucleus although not a conduction pathway, was almost always spared. In contrast, the descending nucleus of the fifth cranial nerve showed definite inflammatory changes, even though the adjacent tract was spared.

In the middle and caudal regions of the medulla the general pathologic picture was similar to that at the higher levels, although much less severe. The intensity of the tissue reaction tended to decrease as one descended until the pyramid decussation was reached, at which point the changes again increased in severity. In this middle portion of the medulla the predominance of destruction appeared to be limited to the ventral reticular formation and the area of the nucleus of the twelfth cranial nerve. The latter cell group might appear structurally intact, in spite of a moderately severe inflammatory reaction in the adjoining tissues (fig. 2 *b*).

In the lower portion of the medulla, at the level of the pyramidal decussation, the severity of the inflammatory reaction again increased and tended to localize ventral to the decussation, in the region of the nucleus of the eleventh nerve (fig. 2 *c*). The cells of this nucleus were usually fairly severely injured (fig 1*A*).

Although the inflammatory reaction comprised the most striking histologic feature of bulbar poliomyelitis, it played a relatively minor role in the clinical picture. In many cases cranial nerve nuclei implicated by severe inflammatory reactions showed minimal or no actual damage to their cells and no associated clinical dysfunction (fig. 1 *D*). This was particularly true of the nucleus ambiguus and the nucleus of the twelfth cranial nerve, which were often directly involved by extensive inflammation without injury to the cells or impairment of their function.

From our observations it would appear that only when the inflammatory reaction is severe enough to result in an inflammatory necrosis of the nuclear groups does one observe actual dysfunction as a result of the inflammation.

DIFFUSE AND FOCAL NEURONAL DAMAGE

The clinical symptoms in bulbar poliomyelitis are dependent directly on the neuronal damage and will therefore vary with the cell groups involved. In order better to understand such a clinical-pathologic correlation, one must first have a knowledge of the normal functional cell groups within the medulla.

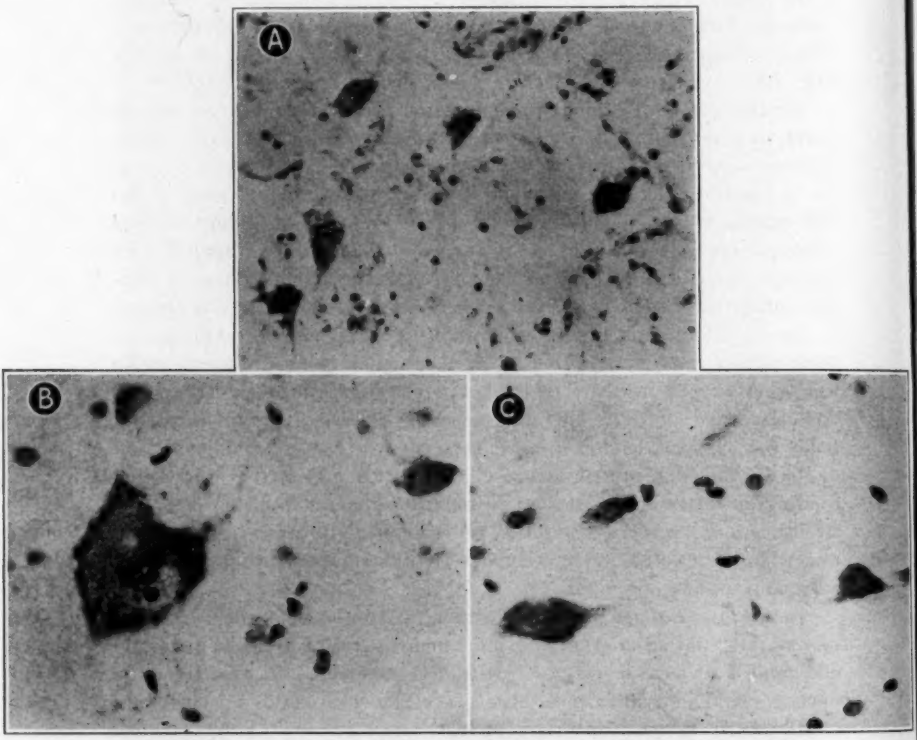

Fig. 3.—*A*, normal cells of the nucleus ambiguus. These cells resemble the anterior horn cells of the spinal cord. *B*, normal large neuron of the medial reticular substance. Note the eccentrically placed nucleus and the finely granular central Nissl substance. *C*, normal cells of the lateral reticular substance. These elements average 10 to 20 microns; their cytoplasm is scanty, and their Nissl substance is poorly defined. Nissl stain.

Normal structure.—The principal nuclear groups in the medulla are the motor and sensory nuclei of the lower four cranial nerves, the reticular nuclei and the inferior olivary complex. The last-named structure is never involved in poliomyelitis. Most of the sensory nuclei of the cranial nerves show only a few scattered cell changes. This is

also true of the dorsal motor nucleus of the tenth cranial nerve and the twelfth nucleus. The nucleus of the eleventh nerve is occasionally involved and can be correlated with clinical symptoms.

The most important nuclear groups in bulbar poliomyelitis are the nucleus ambiguus and the reticular cells. The cells of the nucleus ambiguus are identical with the somatic motor neurons found in the ventral horn of the spinal cord and have been extensively discussed in the literature (fig. 3 *A*).

The cells of the medullary reticular formation may be divided into two groups on the basis of size. The large cells are present in the ventromedial reticular formation, between the nucleus ambiguus and the medial lemniscus. Ventrally they are limited by the inferior olivary nucleus and taper off dorsally, never reaching the dorsal nucleus of the tenth nerve (fig. 4 *a*). This nuclear group is about 14 mm. long, extending from 2 to 3 mm. caudal to the superior pole of the nucleus of the twelfth cranial nerve to the superior pole of the motor nucleus of the seventh cranial nerve, in the pons. It attains its greatest size at the extreme cephalic end of the medulla, where as many as 100 cells may be found unilaterally in a 10 micron section. It tapers in size gradually in both directions. At the level where the greatest number of cells are seen, the nuclear group reaches the midline. In the lower portion of the pons the cells are scattered between the midline and the seventh cranial nerve nucleus.

There are approximately 75,000 to 100,000 large reticular cells on one side in a normal brain stem. They vary considerably in size and shape. The largest are 75 microns in length and have a width of 35 microns. The smallest are 35 by 20 microns, and the mean measurements are 50 by 25 microns. They may be almost spherical, angular, elongated or spindle shaped. The nucleus is vesicular and contains a prominent, eccentrically placed nucleolus (fig. 3 *B*). The Nissl substance, although prominent, varies greatly in form. It is usually finely granular, particularly in the center of the cell. At the periphery, the Nissl substance is frequently in large, prominent clumps. Occasionally a cell is seen the Nissl substance of which greatly resembles that in somatic motor neurons, i.e., large, prominent, equally distributed, box-like granules. It is not uncommon to see a cell in which the Nissl substance is thready. These large reticular cells are very likely to accumulate pigment with age. This pigment is very prominent in many cells of persons past 40 years of age. It frequently occupies almost all of the cell.

Unlike the large reticular cells, the small and medium-sized cells are present throughout the reticular formation of the medulla (fig. 4). They are seen intermingled with the large cells medially but comprise almost exclusively the lateral and dorsal reticular areas. In any one

section the small cells outnumber the large reticular cells by more than 10 to 1. However, since the large cells are not located in the lower and middle portions of the medulla, the total number of small cells is at least twenty-five times that of the total number of large reticular cells.

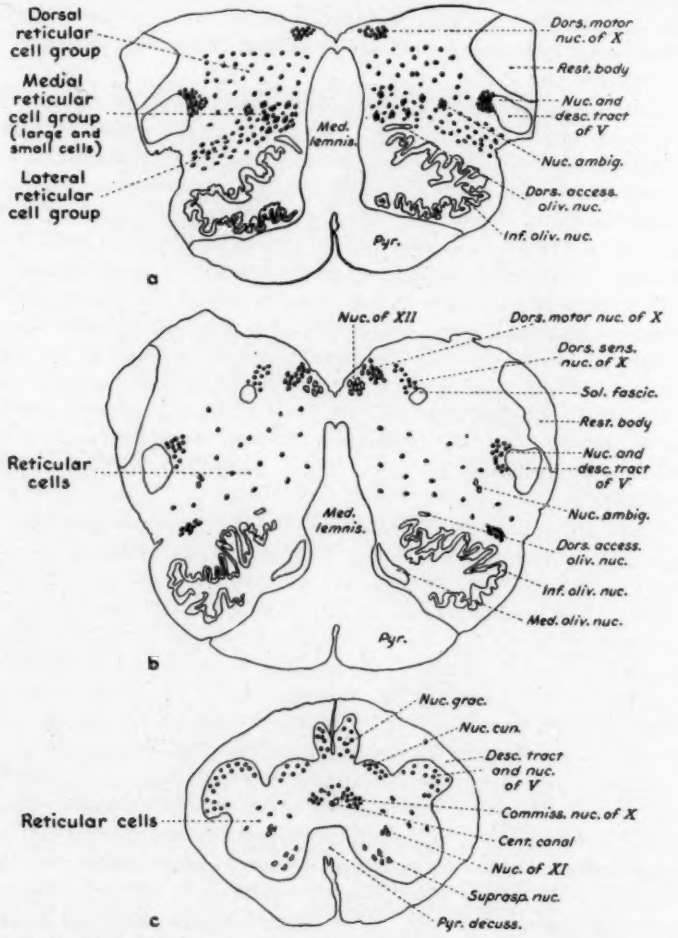

Fig. 4.—Distribution of the cells of the medullary reticular formation. The large cells are situated in the ventromedial region between the nucleus ambiguus and the medial lemniscus. They appear to be limited to the upper medulla (*a*). The small cells are found throughout the reticular formation but predominate within the lateral and dorsal regions (*b* and *c*).

No matter where they are located within the medulla, the small cells exhibit the same general features. They vary from spherical to spindle

shaped. They average 10 microns in width and 20 microns in length, the largest being 15 by 30 microns and the smallest 8 by 8 microns. The nucleus is large, vesicular and eccentrically placed (fig. 3 *C*) and has a prominent nucleolus. The cytoplasm is scanty, surrounding the nucleus as a narrow band. The Nissl substance is poorly defined, rarely appearing as sharply demarcated, boxlike granules. They usually occur as dark-staining threads and irregular clumps or small, barely visible granules.

It is evident from the foregoing discussion that a great deal of caution must be exercised in interpreting pathologic changes in the reticular cells. Such signs of pathologic alteration as fragmentation and dissolution of the Nissl substance and eccentricity of the nucleus are common in the normal reticular cells. For this reason, the percentages for cell damage cited in our studies are probably lower than the actual figures. The pathologic features relied on were cellular swelling, formation of ghost cells, pyknosis of the nucleus and neuronophagia. Changes in the Nissl substance were not considered unless they were clearcut. In all cases the pathologic reticular cells were carefully compared with those in a normal brain.

Pathologic Studies.—The neuronal changes in general consisted of acute swelling and diffuse or perinuclear chromatolysis. In cases of more severe involvement the cell processes became fragmented and detached, leaving a rounded, swollen, light-staining cell, which was identified chiefly by the still intact nucleus. Later, even the nucleus underwent changes, becoming eccentrically placed, losing its staining properties and eventually showing fragmentation, pyknosis and extrusion from the cell.

The stage of cellular alteration at which neuronophagia occurs depends on the rapidity of the neuronal destruction by the virus. In many cases apparently structurally intact cells became invaded by phagocytes, indicating that the cell, although appearing healthy, had been destroyed by the virus. In most cases, however, neuronophagia occurred in ganglion cells that had obviously been injured, as indicated by their conspicuous anatomic alterations. Neuronophagia was not the usual process, and most of the ganglion cells that were destroyed underwent fragmentation and dissolution without neuronophagia.

On the basis of the predominant functional injury to the cell groups of the medulla, it is possible to divide bulbar poliomyelitis symptomatically into four types: (1) involvement of the nucleus ambiguus, (2) involvement of the small reticular cells, (3) involvement of the large reticular cells and (4) damage to both the small and the large reticular cells.

1. Nucleus Ambiguus: In this group the neuronal damage was limited to the motor nuclei of the cranial nerves, even though diffuse mesodermal-glial reaction was also present. There were only 3 cases in which this nuclear group was exclusively involved, since most patients with damage of this type will recover under adequate therapy. The involvement of the nucleus ambiguus was extensive in each case and variable in degree. In some of the cases there was associated damage of the nuclei of the eleventh and twelfth cranial nerves.

Clinically the primary manifestation in these cases was difficulty in swallowing and talking. There were pooling of secretions in the throat and occasionally regurgitation of fluids through the nose. Speech was often nasal in quality or hoarse from faulty innervation of the vocal cords. An occasional patient was unable to talk. In some patients there appeared to be a definite dissociation of these two complaints, some patients being able to swallow but having difficulty in speech, while others had only manifest disturbances in deglutition. Such a dissociation appeared to correlate with the level of involvement of the nucleus ambiguus. When this cell group was injured in the upper part of the medulla, dysphagia was most prominent. Dysarthria resulted chiefly from involvement of the nucleus ambiguus, in the middle portion of the medulla. Generally, however, the entire nucleus was diffusely injured, producing combined symptoms. The total clinical picture was one of pure obstruction to the airway, with death from asphyxia. Fatalities in this group were necessarily small because the patients were supported by having the airway cleared by various therapeutic means.[29]

2. Small Reticular Cells: In this group the predominant neuronal damage was observed within the small reticular elements, which are situated chiefly within the ventrolateral reticular formation (fig. 5 *A*). This area is located primarily in the upper portion of the medulla between the descending root of the fifth cranial nerve and the olivary nucleus. It is bounded medially by the nucleus ambiguus and extends laterally to the surface of the medulla (fig. 4). The cells in this region are generally very small and irregular. Clinically, the patients in this

29. Brown, J. R.; Baker, A. B.; Adams, J., and McQuarrie, I.: The Bulbar Form of Poliomyelitis: I. Diagnosis and the Correlation of Clinical with Physiological and Pathological Manifestations, J. A. M. A. **134**:757 (June 28) 1947. Brown, J. R., and Baker, A. B.: Poliomyelitis: I. Bulbar Poliomyelitis: A Neurophysiological Interpretation of the Clinicopathological Findings, J. Nerv. & Ment. Dis. **109**:54, 1949. Brown, J. R.; Baker, A. B., and McQuarrie, I.: Bulbar Form of Poliomyelitis: II. Therapeutic Measures Based on Pathologic and Physiologic Findings, J. A. M. A. **135**:425 (Oct. 18) 1947. Baker, A. B.: Bulbar Poliomyelitis: Its Mechanism and Treatment, Am. J. Med. **6**:614, 1949.

group showed severe respiratory symptoms consisting of variations in the rate and depth of respiration, often with prolonged intervals between inspirations. There were increasing periods of apnea with Cheyne-Stokes respiration. Terminally there were extreme restlessness, confusion, cyanosis and coma.

A correlation of the structural damage to the small reticular cells with the respiratory and circulatory symptoms is seen in figures 6 and 7.

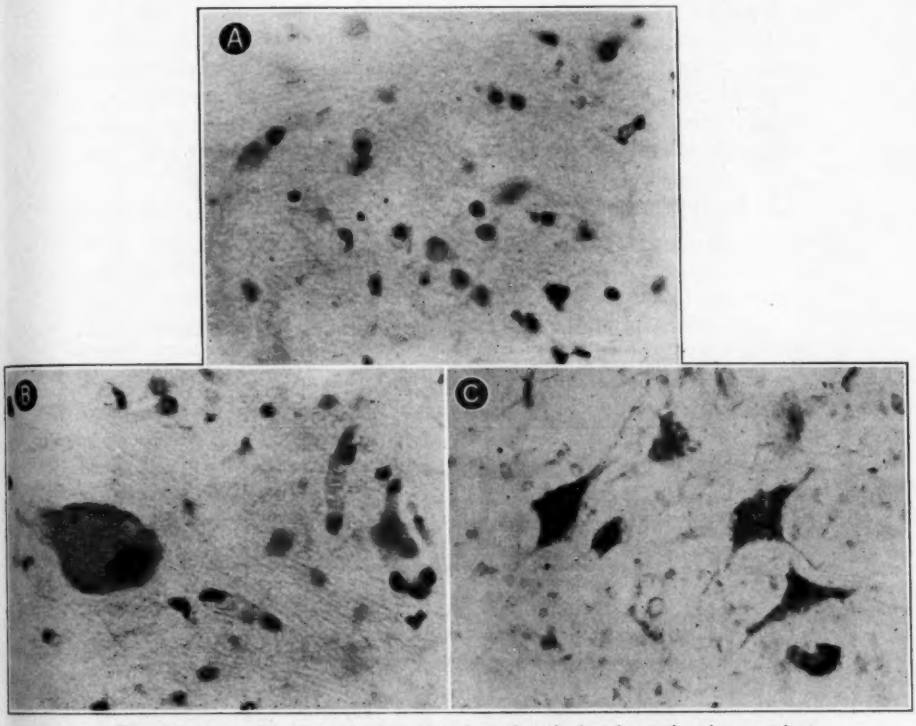

Fig. 5.—*A*, section through the ventrolateral reticular formation in a patient who died of respiratory failure. All the small reticular neurons have undergone complete degeneration. *B*, section through the medial reticular formation in a patient who died of circulatory collapse. Note the chromatolysis and the nuclear pyknosis of the large reticular neuron. *C*, nucleus ambiguus from a patient who recovered from severe pharyngeal and laryngeal paralysis. All the nerve elements present appeared structurally intact. Nissl stain.

Figure 6 is a tabulation of the damage to the small cells in relation to the degree of the respiratory symptoms for all patients for whom clinical evidence of such a disturbance was available. For comparison, figure 7 is a similar correlation of the damage to the small cells and the circu-

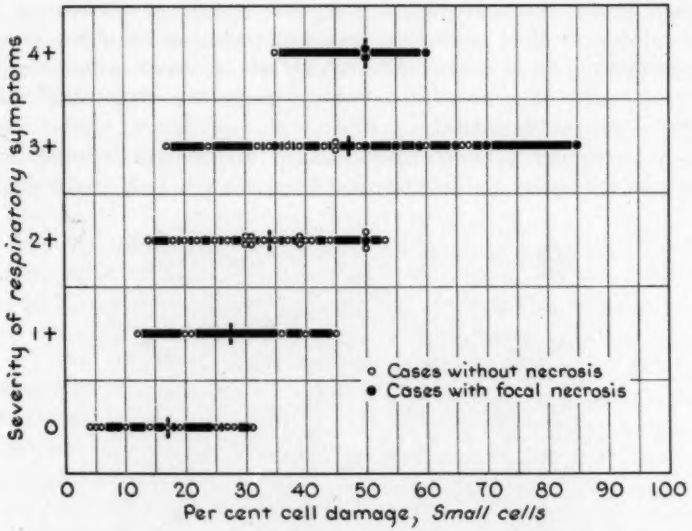

Fig. 6.—Relation of damage to the small cells of the reticular formation to the degree of severity of respiratory symptoms. There is a definite correlation between the severity of the cell damage and the intensity of the clinical symptoms.

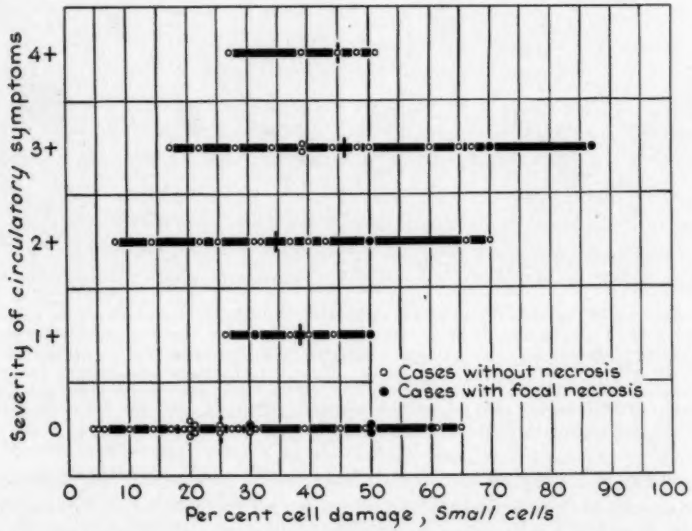

Fig. 7.—Relation of damage to the small reticular cell to circulatory disturbances. As many as 65 per cent of the small cells can be structurally damaged without producing circulatory symptoms.

latory symptoms. These charts show that there is a definite correlation between the damage to small cells and the respiratory symptoms, whereas there is no correlation between such damage and the circulatory symptoms. It is well accepted that the anatomic alterations within the nerve cells in poliomyelitis do not indicate the actual functional impairment that has occurred. The actual functional damage will be much greater than the structural alteration. However, from figure 6 it is apparent that one can actually have structural alteration in at least 31 per cent of the small reticular cells without any clinical evidence of respiratory dysfunction. From our studies it would seem that this localized cell group is susceptible to injury in poliomyelitis and comprises one of the most specific centers of involvement in this disease. It would appear that such neuronal damage in the ventrolateral reticular cells can be almost exclusively correlated with involvement of respiratory control.

3. Large Reticular Cells: The large reticular elements of the medulla are situated ventromedially. Although many smaller reticular cells were also damaged in this region, because of their predominance more laterally, their total damage was proportionately less severe. It is our impression, therefore, that the symptoms produced by damage to this area were the result of the injury to the large cells (fig. 5 *B*).

In all patients with damage to these cells failure of circulation was the principal clinical finding. The pulse rate was rapid and out of proportion to the increase in temperature. The rhythm was irregular and the pulse thready. The blood pressure varied from high to low levels, and the pulse pressure was very small, being as low as 10 mm. of mercury. Anxiety and restlessness were always present. As circulatory failure progressed, the blood pressure dropped to shock levels, the pulse became imperceptible and the skin became cold and clammy, with mottled cyanosis. Terminally there were delirium, coma and hyperthermia.

In figures 8 and 9 the structural damage to the large cells of the ventromedial reticular formation is correlated with the intensity of the respiratory and circulatory symptoms, respectively. Figure 8 shows a definite correlation of the degree of damage to the large cells and the circulatory symptoms; on the other hand, figure 9 shows that there is no correlation of the damage to the large cells and the respiratory symptoms. It appears fairly evident from these studies that the large cells of the reticular formation specifically are related to vasomotor regulation and probably comprise the center for circulatory control in the medulla. Although it is impossible to evaluate the total functional damage to such centers from the actual structural observation, it appears from our studies (fig. 8) that at least 19 per cent of these large cells can be damaged structurally before the appearance of any clinical symptoms.

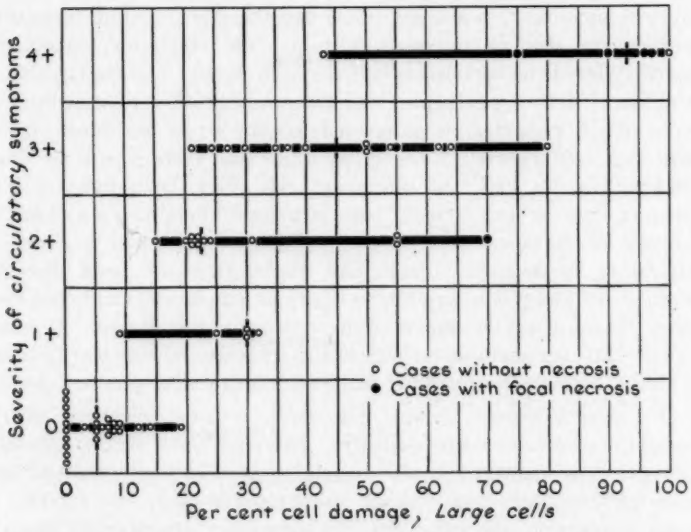

Fig. 8.—Relation of damage to the large reticular cells to the degree of circulatory symptoms. Note the definite correlation between the severity of the cell damage and the intensity of the vasomotor disturbances.

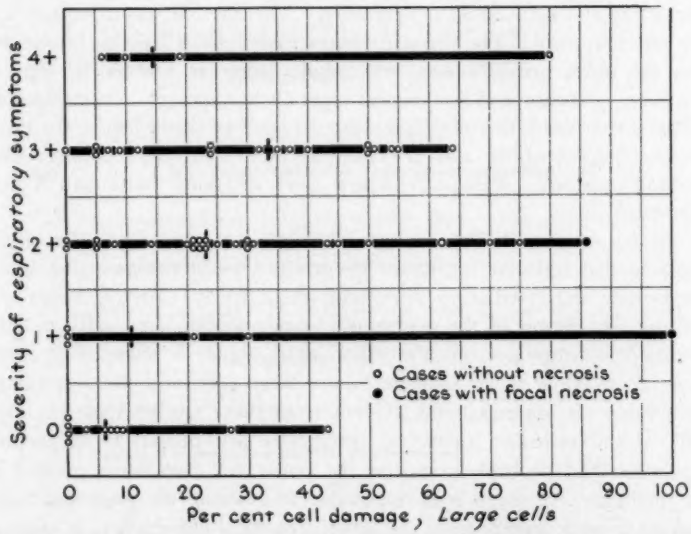

Fig. 9.—Relation of damage to the large reticular cells to the intensity of respiratory disturbances. There appears to be no correlation between these two factors, thus indicating that the large reticular cells play no part in respiratory function.

4. Damage to Both Small and Large Reticular Cells: In spite of the tendency of the pathologic process in many cases of bulbar poliomyelitis to select specific cell groups in the medulla, a large number of patients in our series showed very severe implication of most of the reticular cells. When such severe damage to both the large and the small reticular cells occurs, the clinical course is a fulminating one, and death usually occurs within a few hours or a few days after the onset of the illness. It is for this reason that a large number of patients with fatal bulbar poliomyelitis fall in this group. Because of the rapid course of the illness, it was impossible to determine accurately the predominance of either circulatory or respiratory symptoms. Patients in this group were necessarily excluded from our clinical correlations in figures 6 to 9.

Chronic Changes: In 4 cases autopsy showed little structural alteration in any of the medullary cell groups. The inflammatory process was extremely mild, and in 2 cases gliosis was already visible. Reference to the histories revealed that all the patients had had severe bulbar symptoms with predominant involvement of the cranial nerve nuclei and obstructive symptoms. All patients survived the acute illness and died one to four months later of pulmonary complications. The relative absence of medullary changes was no doubt due to the chronicity of the process with recovery of functionally damaged elements. These cases are particularly instructive in demonstrating the reversibility of the neuronal damage in many cases of medullary poliomyelitis (fig. 5 *C*).

FOCAL MEDULLARY INVOLVEMENT

Focal involvement of the medulla in poliomyelitis, although dramatic in appearance, actually is of no greater importance than the degree of concomitant neuronal damage. This type of lesion, however, enables one to visualize grossly certain functional areas of medullary damage, and, therefore, we describe it under a separate head. Cases of this type are unusual in that during the infectious process there results a focal inflammatory necrosis which can be demonstrated readily with special stains. Because these areas of involvement tend to destroy all the underlying nerve cells, they produce characteristic clinical pictures, depending on their location in the medulla. If the lesions are situated laterally, there results disturbed respiratory control because of involvement of the small cells in the ventrolateral reticular formation. If the focal lesions are situated more medially, there result vasomotor symptoms, probably due to destruction of the large cells of the ventromedial reticular substance. Additional neuronal damage may occur in cells other than those destroyed by the focal areas of necrosis, and in such cases the clinical picture will be more complicated.

In our material there were 7 cases of focal damage in which the predominant symptoms were circulatory. The lesions were superim-

posed on each other after the sections of the medulla were enlarged on an Edinger projector (fig. 10). A similar procedure was followed for 17 cases in which respiratory symptoms were most pronounced (fig. 11).

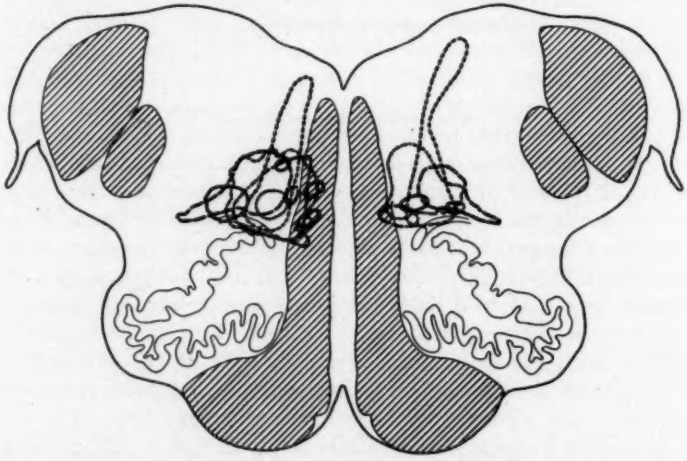

Fig. 10.—Location of areas of focal necrosis in the brains of 7 patients with bulbar poliomyelitis who died of circulatory failure. Note that all the damage is localized to the medial reticular region, where the large reticular cells are situated.

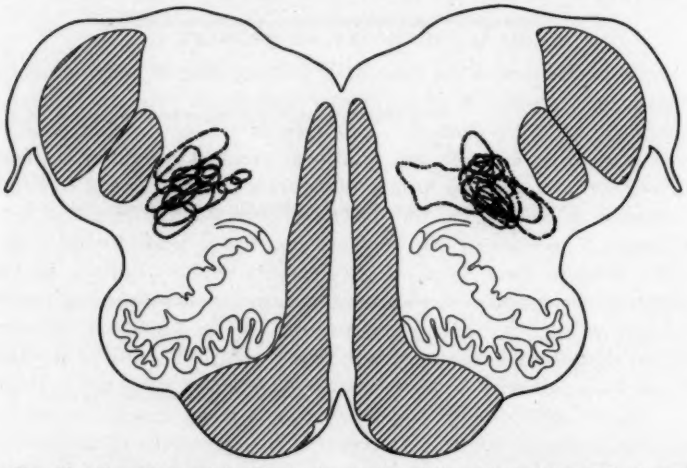

Fig. 11.—Superimposed lesions in the brains of 17 patients who died of paralysis of the respiratory muscles. The lesions are all situated laterally in the region of the small reticular cells.

It is readily apparent from figure 10 that in all cases with vasomotor symptoms the lesions were situated in the ventromedial reticular formation in that area in which the large cells predominate. When the areas

of focal damage are charted in cases of respiratory failure, they appear to be situated in the ventrolateral reticular area involving the smaller cells. These observations offer additional evidence concerning the specific function of the various cell groups within the medulla. *A* and *B* of figure 12 are photomicrographs showing the actual appearance of these focal areas of damage.

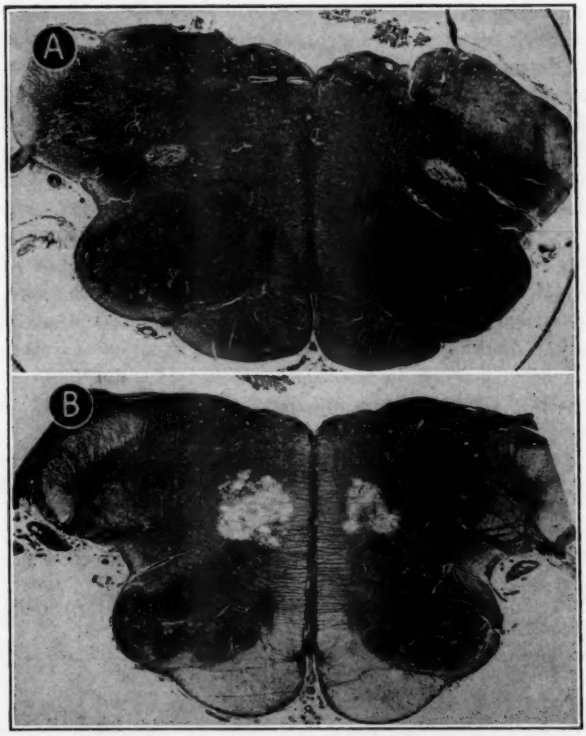

Fig. 12.—*A*, bilateral focal areas of inflammatory necrosis within the lateral reticular region of the upper portion of the medulla of a patient who died of respiratory failure. *B*, bilateral focal areas of necrosis within the medial reticular region of a patient who died of circulatory failure. Weil stain.

COMMENT

Although the present studies were initiated in cases of bulbar poliomyelitis, their ramifications appear to be of even greater significance, since they seem to throw additional light on the physiology of respiration and cardiac control in man. It has generally been accepted that the medulla plays a major role in coordinating respiration and circulation,

since section of the nervous system above the medulla does not alter respiration if the vagus nerves are intact (Marsh [30]; Wold [31]). However, few studies are available which would identify specific autonomic function with discrete centers or cell groups in the medulla of man. Almost all the early studies on the medullary centers have necessarily been limited to animals.

As early as the nineteenth century, Legallios [32] and Flourens [33] showed that damage to the caudal part of the medulla at the apex of the fourth ventricle resulted in disturbance of respiration and cardiac action. Flourens described this area as being 2.5 mm. on either side of the midline in the dorsal reticular formation near the sensory nucleus of the tenth cranial nerve. This region became known as the vital node of Flourens. A number of other earlier investigators placed the respiratory center in other areas of the medulla. Gerard [34] and Schiff [35] expressed the belief that the area of Flourens' vital node could be removed with impunity. They stated the opinion that the respiratory center was situated in the superior part of the ala cinerea. Gierke [36] and Krause [37] later objected to these localizations and stated that this center was more deeply situated, in the region of the fasciculus solitarius. Mislawsky [38] described the respiratory center as situated just beneath the calamus scriptorius, in the depths of the reticular formation and in the region of the hypoglossal nucleus.

As studies on the autonomic centers continued, it became obvious that the respiratory center was a diffuse one, involving the reticular formation of the caudal half of the medulla (von Bechterew [39]; Marck-

30. Marsh, N. P.: Epidemic Anterior Poliomyelitis: Its Symptoms and Treatment, with a Review of Recent Investigation into the Experimental Disease in Monkeys, Brit. J. Child. Dis. **8**:300, 1911.

31. Wold, H.: Statistical Note on Swedish Epidemics of Poliomyelitis, Acta med. Scandinav. **115**:560, 1943.

32. Legallios, C. J.: Expériences sur le principle de la vie, Paris, D. Hantel, 1812.

33. Flourens, J. P. M.: Recherches expérimentales sur les propriétés et les fonctions du système nerveux, Paris, Crevot, 1842; Acad. de Sc. **47**:803, 1858.

34. Gerard, R. W.: Nerve Metabolism, Physiol. Rev. **12**:469, 1932.

35. Schiff, J. M.: Einfluss des verlängerten Marks auf die Athmung, Arch. f. d. ges. Physiol. **3**:624, 1870.

36. Gierke, H.: Die Theile der Medulla Oblongata, deren Verlet: Zung die Athembewegungen hemmt, und das Athemcentrum, Arch. f. d. ges. Physiol. **7**:583, 1873.

37. Krause, P.: Zur Histologie des Nervensystem bei akuter epidemischer Kinderlähmung, Deutche med. Wchnschr. **36**:2364, 1910.

38. Mislawsky, N.: Zur Lehre vom Atmungscentrum, Centralbl. f. d. med. Wissensch, 1885, p. 465.

39. von Bechterew, W.: Ueber die Längsfaserzüge der Formatio reticularis medullae oblongatae et pontis, Neurol. Centralbl. **4**:337, 1885.

wald and Kronecker [40]; Marinesco and Gad [41]; Arnheim [42]). This view has been amply substantiated and confirmed more recently through the stimulation of these medullary areas, using needle electrodes placed in the interior of the brains of cats, dogs and monkeys.

Although it is fairly well accepted that the autonomic centers of the medulla are represented by the reticular formation, attempts to differentiate the reticular formation into areas serving specific phases of control have led to conflicting results. Gesell, Bricker and Magee [43] and Brookhart [44] failed to identify any anatomic grouping of the cells in the reticular formation. Brookhart thoroughly explored the reticular formation in 57 dogs and was unable to outline a specific inspiratory or expiratory center. On the other hand, Monnier,[45] using stimulating electrodes, concluded that the ventral reticular substance is the regulating center for inspiratory posture, while the dorsal reticular formation is the regulating center for expiratory posture.

Finally, Pitts and his associates,[46] in a series of experiments on cats and monkeys, outlined excellently the organization of the respiratory center in the medulla. They stated the belief that the respiratory center encompasses the medial and lateral reticular fields, extending from the posterior border of the auditory tubercles, rostrally, to the obex, caudally. This center is bilateral, extending from the midline to the restiform body. By means of localized stimulation, they concluded that the dorsal reticular formation in the cat controlled expiration, while the ventral reticular formation regulated inspiration. The only study of the respiratory center in man was made by Findley.[47] He observed 2 patients who died of central respiratory failure, and in each there were large focal lesions in the reticular formation.

Our present observations would seem to provide final proof of the presence of specific medullary centers for the regulation of respiration

40. Marckwald, M., and Kronecker, H.: Verhandlungen der physiologischen Gesellschaft zu Berlin, Arch. f. Anat. u. Physiol., 1880, p. 441.

41. Marinesco, G., and Gad, J.: Recherches expérimentales sur le centre respiratoire bulbaire, Compt. rend. Acad. d. sc. **115**:444, 1892.

42. Arnheim, R.: Beiträge zur Theorie der Athmung, Arch. f. Anat. u. Physiol., 1894, p. 35.

43. Gesell, R.; Bricker, J., and Magee, C.: Structural and Functional Organization of the Central Mechanism Controlling Breathing, Am. J. Physiol. **117**:423, 1936.

44. Brookhart, J. M.: The Respiratory Effects of Localized Faradic Stimulation of the Medulla Oblongata, Am. J. Physiol. **129**:709, 1940.

45. Monnier, M.: Physiologie des formations réticulées: II. Respiration effets de l'excitation faradique du bulbe chez le chat, Rev. neurol. **69**:517, 1938.

46. Pitts, R. F.; Magoun, H. W., and Ranson, S. W.: Localization of the Medullary Respiratory Centers in the Cat, Am. J. Physiol. **124**:673, 1939; Origin of Respiratory Rhythmicity, ibid. **124**:654, 1939.

47. Finley, K. H.: The Neuro-Anatomy in Respiratory Failure: Report of Two Cases, Arch. Neurol. & Psychiat. **26**:754 (Oct.) 1931.

in man. They appear to substantiate the observations of Pitts and his co-workers, namely, that the various cells of the reticular formation of the medulla have a definite anatomic grouping, each group subserving a specific clinical function. In man, at least, the respiratory center appears to be localized to the small cells of the ventrolateral reticular formation. This is a paired center situated primarily between the descending root of the fifth cranial nerve and the inferior olivary nucleus. It extends from the superior pole of the twelfth nucleus to the bulbopontile junction. Focal areas of inflammatory necrosis destroying primarily these centers in poliomyelitis invariably result in clinical evidence of failure of central respiratory control, namely, irregular rhythm and depth of respiration with a tendency to shallowness and prolonged intervals between inspirations. These symptoms progress to periods of apnea and, finally, cessation of respiration. From our studies it would appear that adequate allowance has been made for the protection of these centers. At least 31 per cent of these small reticular cells may be destroyed without precipitating clinically detectable alterations in respiration. From our studies on man it was not possible to differentiate between an inspiratory and an expiratory center for respiration.

Our observations on the circulatory center might also bear comment. In 1939 Wang and Ranson,[48] by stimulation experiments on cats, elicited strong pressor responses from the dorsomedial reticular substance at the level of the inferior fovea and the inferior olivary nucleus. Depressor responses were more diffuse than the pressor responses and were located in the dorsolateral and the ventromedial reticular substance. Certainly, our observation on man tend to substantiate in part the observations of Wang and Ranson. It would appear from our studies that the medullary vasomotor center in man is restricted to the large reticular cells of the ventromedial reticular substance. Bilateral focal necrosis situated just lateral to the midline, and destroying these cells, invariably produces clinical symptoms ascribable to the failure of central control of circulation. The pulse becomes very rapid, often irregular and at times difficult to palpate. The blood pressure may be elevated or may have a downward trend and become unobtainable. The pulse pressure is low. Terminally, the patient goes into shock, with cyanosis, cold skin and hyperthermia. The cells of this nuclear group are very large, measuring 50 microns in diameter, and number about 100,000 on each side. Because of their relatively smaller number (as compared with the cells regulating respiration), destruction of a minimum of 19 per cent of these large cells will precipitate vasomotor symptoms.

Invariably, when the course of the bulbar poliomyelitis was fulminating, with death within a short period, both the medial and the lateral

48. Wang, S. C., and Ranson, S. W.: Autonomic Responses to Electrical Stimulation of the Lower Brain Stem, J. Comp. Neurol. **71**:437, 1939

cell groups were extensively destroyed. The course of the illness seemed to be much longer and less stormy when the lateral cell group or the respiratory centers alone were involved.

There is no question that the rostral levels of the brain, including the pons, midbrain, diencephalon and cortex, play a modifying role in breathing. The degree of involvement of these higher centers in bulbar poliomyelitis warrants further elucidation and will comprise the material for a later report.

CONCLUSIONS

A detailed histologic study of the entire medulla was undertaken in 80 cases of bulbar poliomyelitis, and the pathologic alterations were correlated with the clinical symptoms.

On the basis of the predominant functional injury to the cell groups in the medulla, it is possible to divide bulbar poliomyelitis symptomatically into four types: (1) involvement of the nucleus ambiguus, (2) involvement of the small reticular cells, (3) involvement of the large reticular cells and (4) damage to both the large and the small reticular cells.

The function of the nucleus ambiguus is well known, and its involvement results in dysphagia and dysarthria. The small reticular cells, situated in the ventrolateral reticular area, regulate respiratory function. Their involvement results in irregular rhythm and depth of respiration, periods of apnea and, finally, cessation of respiration. The large reticular cells, situated in the ventromedial reticular area, regulate circulation. Damage to these cells invariably produces clinical symptoms of vasomotor disturbance, such as irregular, feeble pulse, low pulse pressure, irregularities of blood pressure and terminal shock.

When death in bulbar poliomyelitis is rapid, invariably both the circulatory and the respiratory centers in the medulla are severely damaged.

Division of Neurology, University of Minnesota Medical School.

LEPTOMENINGEAL CHANGES ASSOCIATED WITH LIPOCHONDRODYSTROPHY (GARGOYLISM)

Report of a Case

KENNETH R. MAGEE, M.D.
ANN ARBOR, MICH.

SINCE Hurler's [1] description of 2 cases in 1919, a syndrome consisting of enlarged, abnormally shaped head, dwarfishness, grotesque facies with sunken nasal bridge, cloudiness of the corneas, hepatosplenomegaly, umbilical and inguinal hernias, dorsolumbar kyphosis and flexion deformities of the extremities has been recognized. It has been known, under various names, as gargoylism, Hurler's syndrome, Hunter's syndrome, lipochondrodystrophy, osteochondrodystrophy and dysostosis multiplex. Although it is often referred to as Hurler's syndrome, Hunter [2] two years prior to the publication of Hurler's paper described the condition in two brothers.

To date, approximately 100 cases of lipochondrodystrophy have been described in the literature. However, in this large number of reports there have been only 14 comprehensive general pathologic studies and 8 analyses of the changes in the nervous system. On such meager studies, the prevailing opinion places lipochrondrodystrophy in the group of lipid storage diseases related to amaurotic familial idiocy and to the Niemann-Pick and Hand-Schüller-Christian forms of lipid dystrophy.

It is not the purpose of this report to present a comprehensive analysis of the alterations in the central nervous system in this condition. Unfortunately, postmortem changes in my material preclude accurate detailed analysis of the neuronal changes themselves. However, I have had the opportunity of studying the brain in a case in which the unusual aspect was the extensive, spectacular changes in the leptomeninges, a feature never before described in this condition.

From the Division of Neurology of the Department of Medicine, the University of Chicago Clinics, Chicago.

1. Hurler, G.: Ueber einen Typ multipler Abartungen vorwiegend am Skelettsystem, Ztschr. f. Kinderh. **24**:220, 1919.

2. Hunter, C.: A Rare Disease in Two Brothers, Proc. Roy. Soc. Med. **10**: 104, 1917.

REPORT OF CASE

History.—T. C., a 20 month old infant, was admitted to the pediatric service of the University of Chicago Clinics on May 12, 1946. He was born after a forty-two week gestation period and ten hours' labor. The presentation was cephalic, and no instruments were used. There were no complications for either mother or child except that the child vomited frequently for the first few days. The patient had never been able to sit, stand or talk but could raise himself on his elbows and hands. His first tooth appeared at the age of 6 months. The parents stated that the child was underdeveloped except for an abnormal enlargement of the head, which had been noted since the age of 2 months. He had no appetite for solid food, and except for the first two days of his life, during which he received breast milk, he had taken his food only by bottle. Since birth he had had frequent infections of the upper respiratory tract with profuse nasal discharge. During the winter he had a continuous low grade fever and frequent episodes of nausea and vomiting. The parents noted an abnormal curvature of the spine, bilateral inguinal hernia and an umbilical hernia at about the age of 3 months. He had chickenpox when he was 16 months old; there had been no other illnesses or injuries.

The patient had three brothers. One, aged 7 years, had been in normal health except for measles encephalitis at the age of 4 years; this illness left no residual abnormality. Another brother died at the age of 5 months. He had a deformity diagnosed as hydrocephalus at the age of 6 weeks; he was said to have had "a short, snub nose" and to have "snorted all the time." The third brother, aged 3 years, was similar in all respects to the patient and was seen in the pediatric clinic at the same time. He is still alive at the time of this report.

Examination.—The patient was chronically ill. His mental development was obviously greatly retarded. The physical appearance was striking (fig. 1). The head was noticeably enlarged, measuring 53 cm. in circumference, and was long, square and flattened. The anterior fontanel measured 4 by 3 cm. The face was unusual, the bridge of the nose being sunken, the eyes widely spaced and the lips broad and thick. The chest was small and symmetric and showed a pronounced funnel breast deformity. The abdomen was large and protruding. A bilateral inguinal and an umbilical hernia were observed. The liver was palpable 3 cm., and the spleen 2 cm., below the costal margin. Marked dorsolumbar kyphosis was observed, and there was pronounced limitation of motion of the elbows and knees on both sides. The long bones were short and heavy. Several swollen posterior cervical lymph nodes and a large solitary axillary lymph node were noted on each side. His weight was below average (1,005 Gm.) and seemed to be mostly concentrated in the head. Examination of the cornea revealed a bilateral filmy smoky appearance with a shallow anterior chamber. The fundi could not be seen. There was a profuse thin mucous nasal discharge. He snorted and held his mouth open constantly. The heart was normal, with a rate of 110 per minute.

Laboratory Examination.—A blood study disclosed 3,350,000 red cells, 12 Gm. of hemoglobin per hundred cubic centimeters and 11,500 white cells, with a differential count of 44 per cent polymorphonuclear leukocytes, 53 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophils. Serum cholesterol was 272 mg.; serum calcium 11.8 mg. and serum phosphorus 3.33 mg., per hundred cubic centimeters; the glucose tolerance test was normal. Reactions to the Wassermann and tuberculin tests were negative. Urine was normal except for a moderate amount of acetone, present only in the initial examination. Cultures from the nose and throat were normal. The sternal bone marrow showed no abnormality.

The spinal fluid was clear and colorless and under normal pressure; the manometric responses were normal; the cell count was 3 lymphocytes per cubic

millimeter; the Pandy reaction for globulin was negative. The protein measured 25 mg.; the chlorides 668 mg. and glucose 70 mg., per hundred cubic centimeters. The reaction to the Wassermann test was negative; the Lange gold curve was 0000000000, and cultures were sterile.

Roentgenographic examination of the skull revealed diastasis of the coronal sutures with erosion of the outer table of the skull in the occipital region. The

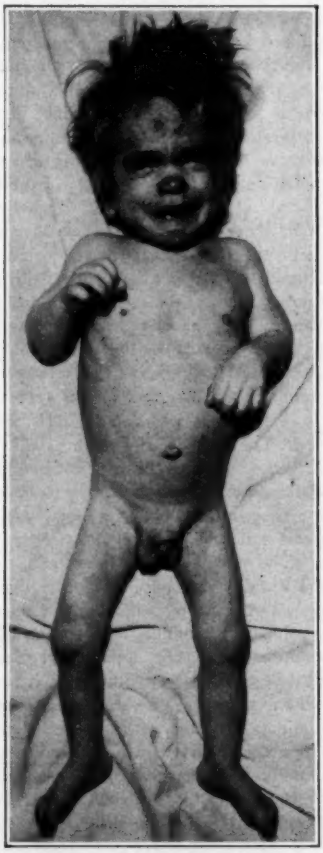

Fig. 1.—Patient at the age of 20 months.

roentgenogram of the spine showed kyphosis, most prominent at the level of the second lumbar vertebra, with deformity of the body of this vertebra.

Course of Illness.—The patient was discharged, at the age of 21 months, on June 12, after the diagnostic study was completed. He was admitted to the Dixon State Hospital on June 21. His course in the institution was marked by frequent attacks of bronchitis, rhinitis and tonsillitis, one attack of bronchopneumonia and one attack of bacillary dysentery. On March 4, 1947, he became somnolent and stayed in a stuporous, drowsy condition until his death. There were no signs of

meningitis, and he was easy to arouse. His temperature was between 99 and 100 F. until March 10, when it rose to 102 F. Edema of the left hand and foot developed on March 4 and 5. On March 6 this edema had disappeared; instead, there was edema of the parietal and occipital regions on the right side. Examination of the ears revealed no abnormality.

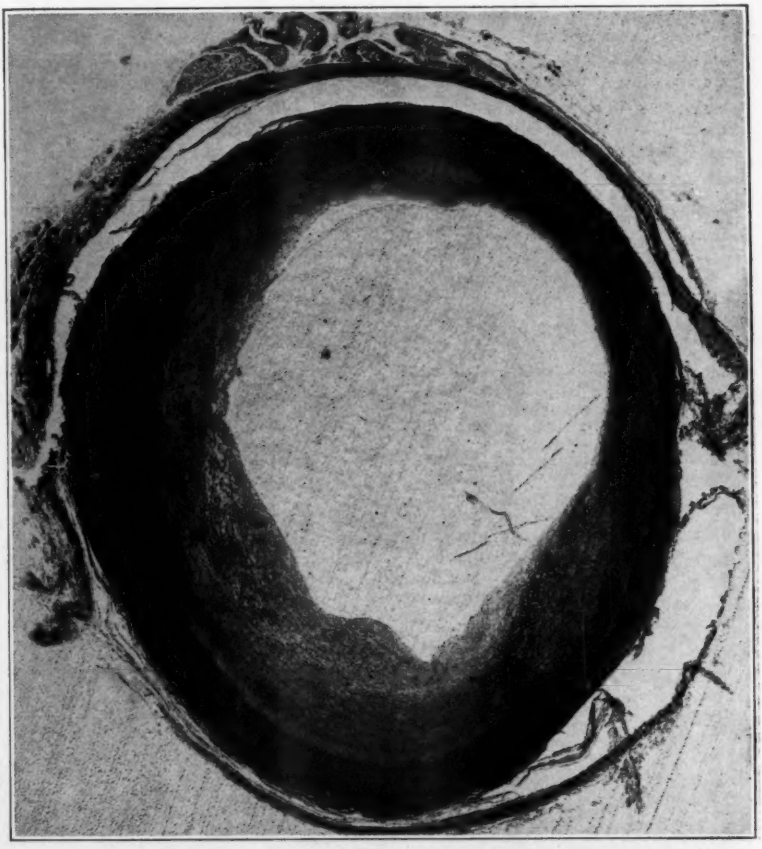

Fig. 2.—Aorta, showing thickened intima. Hematoxylin-eosin stain; × 13.

At this time the liver and spleen were not palpable. There was very slight proteinuria. Blood studies disclosed 3,350,000 red cells, 47.5 Gm. of hemoglobin per hundred cubic centimeters and 14,900 white cells, with a differential count of 46 per cent polymorphonuclear leukocytes, 39 per cent lymphocytes, 5 per cent monocytes and 9 degenerated cells.

On March 11 terminal bronchopneumonia of the lower lobe of the left lung developed, with a temperature between 99 and 101 F. On March 12 he showed pronounced edema of both hands and feet, of his left leg and around his eyes. He became extremely weak, could hardly cry and died the same evening.

ANATOMIC STUDIES

General Examination.—Autopsy revealed extensive involvement of the organs, characterized in sections stained with hematoxylin and eosin by the presence of pale bluish macrophages with small dark nuclei. In many areas the presence of these macrophages was accompanied with a diffuse increase in connective tissue.

Certain structures showed prominent changes. The aorta had an irregularly thickened and fibrotic intima, which in places was twice the width of the media.

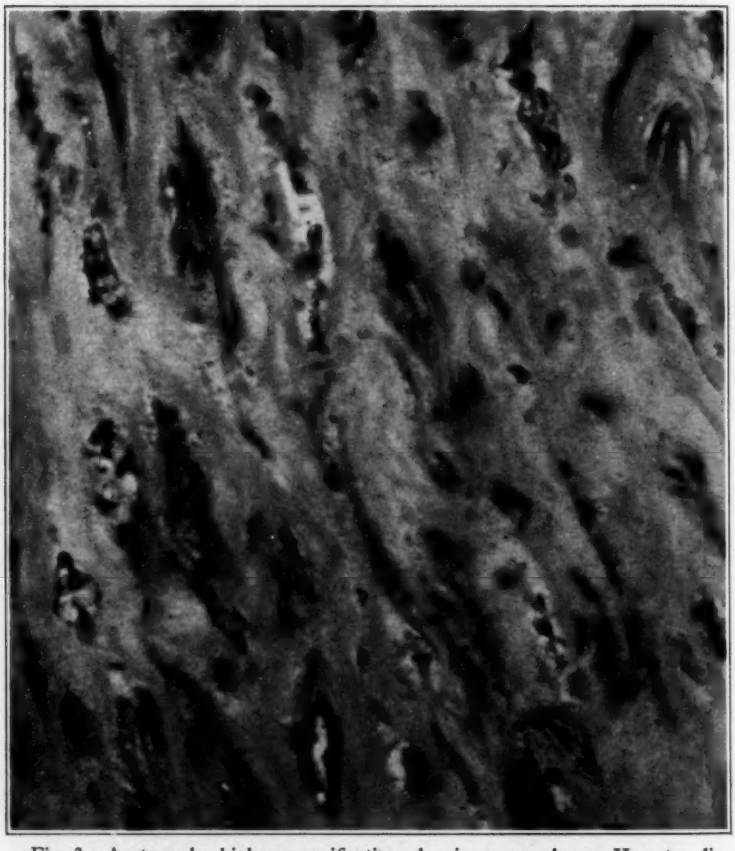

Fig. 3.—Aorta under higher magnification, showing macrophages. Hematoxylin-eosin stain; × 500.

The adventitia was dense, while the media revealed a decrease in muscle fibers and a swollen, acidophilic tunica elastica. Macrophages, similar to those previously described, were seen in all layers (figs. 2 and 3). Similar changes were observed in other vessels. A coronary artery was greatly thickened, with a narrow lumen; its adventitia showed tremendous overgrowth of connective tissue, which incarcerated the fibers of the media. The intima was not prominent. Macrophages were present in the thickened vessel wall.

The ventricular endocardium revealed an increase in connective tissue with the accumulation of macrophages. Macrophages were seen in the red pulp lining the splenic sinusoids and in the hepatic triads. The latter also showed proliferation of connective tissue. Numerous macrophages were present in the interstitial connective tissue of the testis and epididymis. A few of these cells were also seen in the perichondrium. All sections of adipose tissue showed myxoserous degeneration.

Brain.—Gross Observations: The only dura remaining on the brain was a strip 3 cm. in width and 12 cm. in length along the median longitudinal fissure. The dura itself was of normal thickness and had a smooth, glistening inner surface. The pia-arachnoid covering the convexity of the left cerebral hemisphere was enormously thickened, or at least adherent to a smooth, opaque, grayish covering of firm tissue, reaching in places an apparent thickness of 0.5 cm. or more. This densely organized tissue completely obscured the convolutional markings of the convexity of the hemisphere like a heavy rind (fig. 4). In places it was mottled

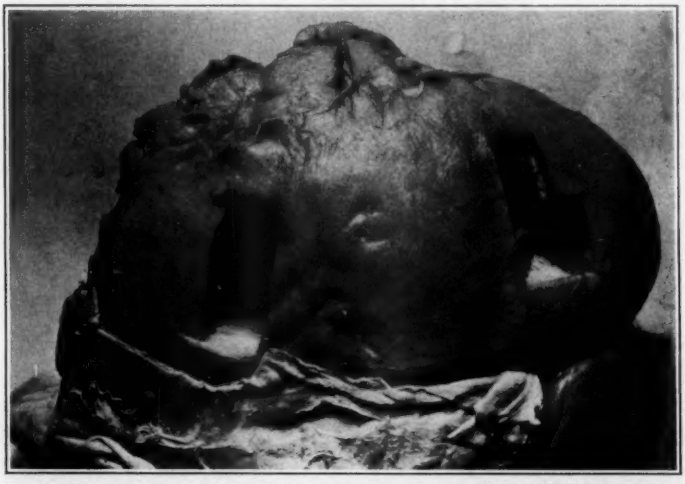

Fig. 4.—Convexity of left cerebral hemisphere, showing thickened leptomeninges.

orange-yellow. The overlying dura had stripped off easily, with no evidence of adhesions from its inner surface to the underlying tissue except near the midline, where there were fine fibrous attachments, which were in places quite tough. A similar, but somewhat thinner, layer of tissue covered the superior and medial portion of the right frontal lobe. This was loosely adherent to the dura near the midline and came off with it.

Laterally and inferiorly the whole right hemisphere was covered with a large, smooth mass, brown in color, with the appearance of a partly inflated football bladder (fig. 5). It extended from the frontal to the occipital pole for a distance of 16 cm. and had a vertical dimension of 9 cm. Its greatest breadth was opposite the parietal lobe, where it measured 7 cm. It compressed and displaced to the left the right cerebral hemisphere, especially the middle and posterior portion. On palpation the mass appeared fluctuant, as though filled by fluid, and was covered on its inner and outer aspects by a thin, smooth, but slightly granular, membrane. The inner and outer leaves of this membrane were fused toward the midline and

became continuous with the thickened arachnoid. The hematoma did not adhere to the normally thin and transparent pia-arachnoid beneath it. The leptomeninges at the base of the brain in the region of the chiasm and interpeduncular cistern were slightly thickened and milky. Except for the compression of the right hemisphere, the external appearance of the brain was not abnormal.

A coronal section through the cerebral hemispheres at the level of the optic chiasm revealed massive displacement of the right cerebral hemisphere and midline structures to the left, with obliteration of the right lateral ventricle and narrowing of the third ventricle and medial part of the left lateral ventricle. The surface of the cortex was flattened, owing to the leptomeningeal changes and the subdural hematoma, but the pattern of the sulci and gyri and the width of the cerebral cortex appeared normal.

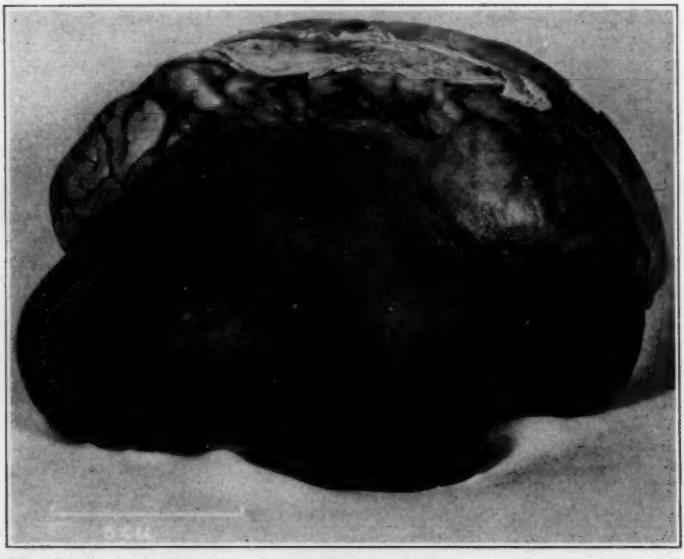

Fig. 5.—Lateral view of right cerebral hemisphere, showing massive subdural hematoma.

Microscopic Observations.—Sections from the meninges and cerebral cortex were obtained and stained with hematoxylin and eosin, cresyl violet, iron hematoxylin, sudan III (C. I. no. 248), sudan IV (C. I. no. 258), nile blue, osmic acid, prussian blue (C. I. no. 1288), the Van Gieson method and the silver methods of Perdrau and Ramon y Cajal. Sections from the midbrain, pons, cerebellum, cervical portion of the cord and celiac ganglion were stained with hematoxylin and eosin and cresyl violet. As a considerable time had elapsed from death to fixation of the brain in solution of formaldehyde U. S. P., postmortem changes were evident in the central nervous system proper, preventing more than a partial evaluation of the findings, but changes characteristic of lipid storage disease were readily evident.

Meninges: The dura was everywhere normal in structure and appearance. The greatly thickened leptomeninges were composed mainly of thick, dense collagenous connective tissue, having the appearance of thickened dura rather than of pia-

arachnoid. A cleft near the middle divided the leptomeninges, but this was not the natural delimitation between pia and arachnoid. The latter could not be distinguished. There was, however, a clear line of cleavage between the leptomeninges and the surface of the cerebral cortex (fig. 6).

Stains with cresyl violet and, particularly, iron hematoxylin revealed large numbers of cells with small, round or oval, dark-staining nuclei arranged between the strands of coarse connective tissue. About these nuclei the outline of a large amount of elongated, nonstaining, reticulated cytoplasm could barely be discerned. The network running through the cytoplasm surrounded numerous small round, nonstaining areas and could be typically described as "honeycombed." The cells had every appearance of being macrophages.

Inserted into the collagenous connective tissue nearer the surface of the cortex were irregular sheets of cells with large heavy-staining, pleomorphic nuclei. The cytoplasm of these cells also did not stain with hematoxylin and eosin, cresyl violet or iron hematoxylin, but with the last two stains the honeycombed outline of the cytoplasm could be discerned. Here the cytoplasm was much fuller, more rounded and polygonal, than the cytoplasm of the cells lying along the interstices between collagen fibers and bundles. In places the cells were so closely packed that large masses of them clustered side by side. Near the periphery the sheets of cells gradually faded out into the connective tissue, and the cells lay between the collagen fibers, as described. Fine strands of connective tissue ran into the densely cellular areas. With silver and Van Gieson stains these strands were seen to be a reticulum of young connective tissue, instead of the large bands of collagenous connective tissue seen elsewhere. The reticular network surrounded the cytoplasm of these cells, more or less making nests for them (fig. 7).

Sections were stained with prussian blue to ascertain how much hemosiderin, if any, was present in the thickened meninges of the left cerebral hemisphere, in view of the massive hematoma on the opposite side. Only a few areas of the leptomeninges near the superficial blood vessels stained for iron.

The less thickened leptomeninges on the lateral surface of the right cerebral hemisphere beneath the hematoma contained a large number of macrophages and exhibited a loose proliferation of collagen fibers. In this location a few scattered macrophages contained blood pigment. The inner membrane of the large subdural hematoma was observed to be composed of the same type of thickened and infiltrated connective tissue.

Frozen sections were stained to ascertain the lipid content of the large reticulated cells. The staining reactions were qualitatively similar, but there was considerable variability in the degree of staining of different cells. In fact, there were great differences in the amount of lipid material stained in different portions of the cytoplasm of each individual cell. Cells of apparent fibroblastic derivation within the collagenous connective tissue showed numerous granules of lipid-stained material deposited in the honeycombed cytoplasm. Some of the cells were completely stained, but others only partially or not at all (fig. 8). Within the densely cellular areas the staining reaction also varied. In nests of closely packed cells, all the voluminous cytoplasm was intensely stained, while in surrounding areas of apparently similar cytologic structure the cells might stain only partially.

Sudan III stained the lipid a bright orange. Sudan IV (Herxheimer) produced a bright red stain. Nile blue did not stain the lipid as well but in the densely cellular areas rendered the cytoplasm a dull pink. Osmic acid produced a very heavy stain of the cytoplasm in the densely cellular areas, but only a small amount of the stain was taken by the cells between the collagen bundles. The most successful staining was produced by the supersaturated isopropanol (isopropyl

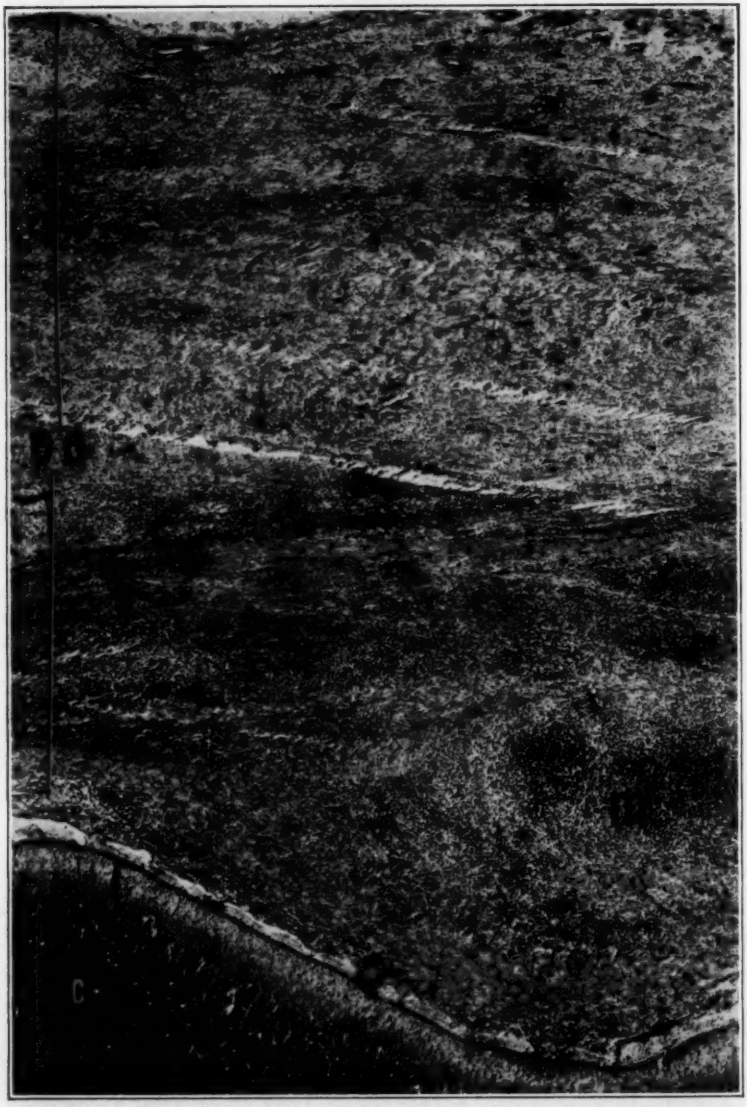

Fig. 6.—Leptomeninges (*pa*), showing thickened dense collagenous connective tissue and relation to surface of cerebral cortex (*C*). Note masses of cells (macrophages, *m*) within heavy meningeal layer. Iron hematoxylin stain; × 32.

Fig. 7.—Leptomeninges, showing reticulum surrounding densely cellular areas. Perdrau silver method; × 430.

alcohol) method with oil red O (C. I. no. 73), as described by Lillie and Ashburn.[3] Both varieties of cells were stained an intense, deep scarlet. However, as already mentioned, there were still staining variations within the different cell groups (fig. 9).

Cerebral Cortex: Sections from the left frontal, parietal and temporal portions of the cortex were stained with cresyl violet and hematoxylin and eosin. The only significant changes consisted of ganglion cell disease, characterized by tumefaction and ballooning of the cytoplasm with displacement of the nucleus and a small

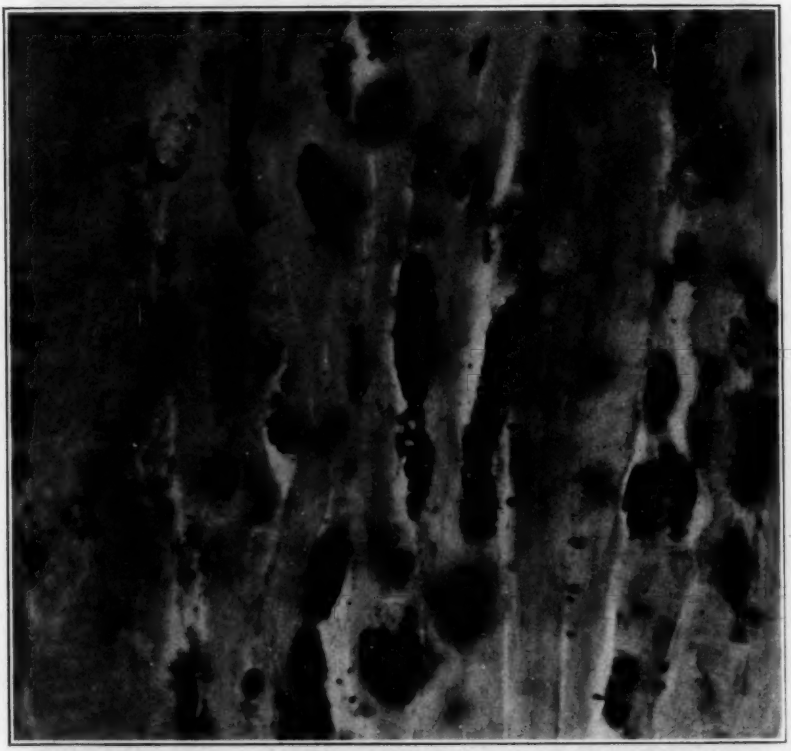

Fig. 8.—Collagenous connective tissue in leptomeninges, showing lipid-stained substance in macrophages. Oil red O; × 630.

amount of remaining Nissl substance at the periphery of the cell body. The cell processes were relatively uninvolved. In some cells the cytoplasm showed a fine honeycombing, while in others it was homogeneous. The appearance was typical of lipid storage disease. Frozen sections stained with sudan III, sudan IV (Herxheimer), nile blue and osmic acid revealed no intracellular or extracellular

3. Lillie, R. D., and Ashburn, L. L.: Supersaturated Solutions of Fat Stains in Dilute Isopropanol for Demonstration of Acute Fatty Degeneration Not Shown by Herxheimer Technic, Arch. Path. **36**:432 (Oct.) 1943.

staining of lipid except for a small amount in the moderately thickened adventitia of the blood vessels. With oil red O there were accumulations of lipid which stained scarlet in some of the larger ganglion cells. The stain was not as intense as in the meninges, nor was it taken so extensively by the cells. The cytoplasm of a few cells was completely stained; the majority showed only a few granules (fig. 10).

Midbrain, Pons and Medulla: The changes here were similar to those in the cerebral cortex. In general, the larger neurons were most affected. Rather pronounced postmortem changes were evident.

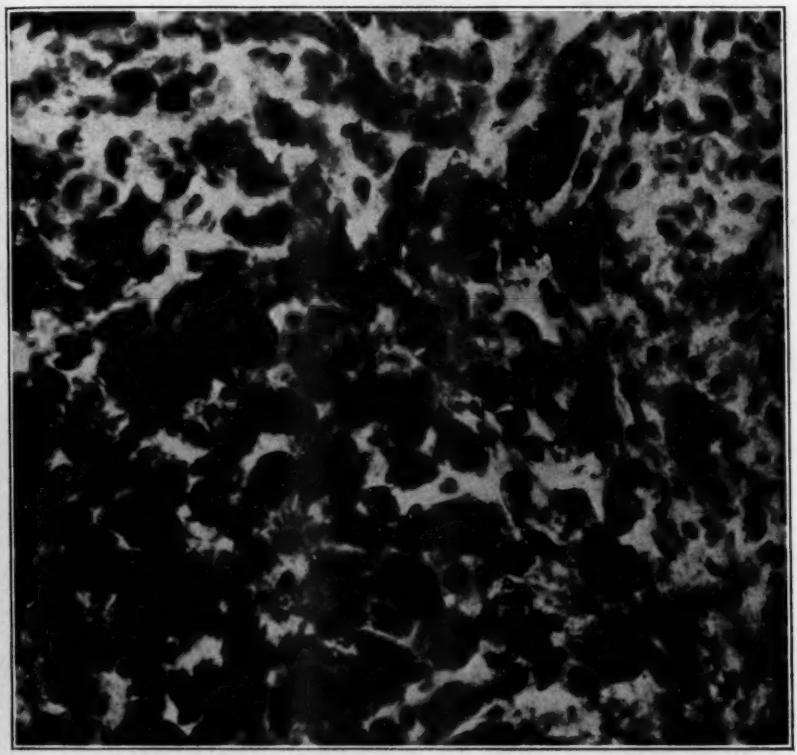

Fig. 9.—Densely cellular area in leptomeninges, showing lipid-stained substance in cytoplasm of macrophages. Oil red O; × 600.

Cerebellum: In the cerebellum there were almost no changes of the type described. The Purkinje cells and the cells of the cerebellar nuclei were remarkably normal, in contrast to the rest of the central nervous system.

Cervical Portion of Cord: Typical changes were observed in the neurons. The ventral horn cells were particularly and spectacularly involved (fig. 11).

Celiac Ganglion: The cell bodies of the postganglionic sympathetic neurons were similarly enlarged and swollen with displaced nuclei.

No increase in glial nuclei, such as would indicate neuroglial sclerosis, could be observed anywhere in the gray or the white matter of the central nervous system.

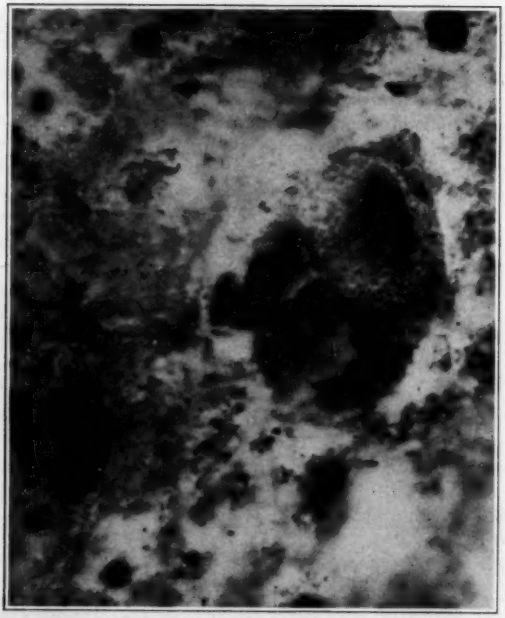

Fig. 10.—Swollen cell body in cerebral cortex, showing lipid-stained deposit. Oil red O; × 1,200.

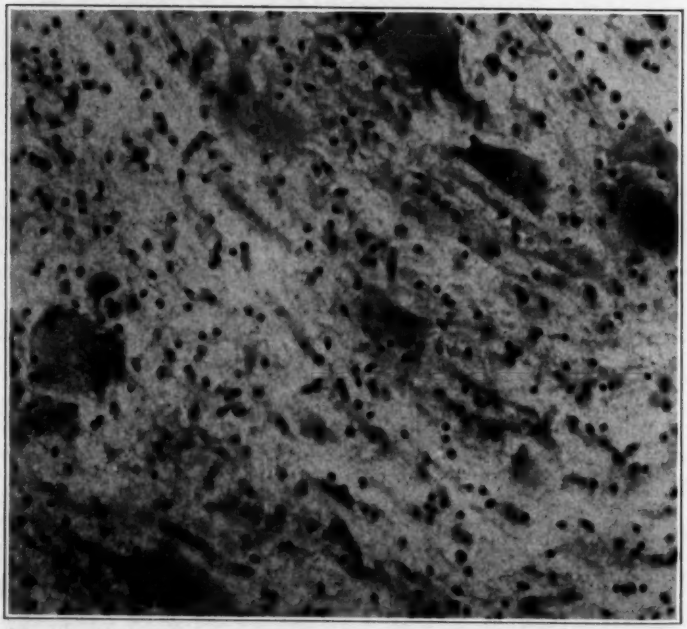

Fig. 11.—Altered anterior horn cells in portion of cervical cord. Cresyl violet; × 290.

COMMENT

Changes such as those described in the leptomeninges have never before been noted in a case of lipochondrodystrophy. The first pathologic report of a case was that of Tuthill,[4] who originally believed that she was describing a case of juvenile amaurotic familial idiocy. The meningeal changes noted by her consisted of slight thickening and the accumulation of granules which stained blue with thionine in the meninges about the base of the brain. According to Tuthill, these particles, also observed inside the neurons throughout the central nervous system, lying free in adventitial spaces and around nerve and glia cells, were thought to be due to associated tuberculous meningitis, with obstruction of the venous return preventing adequate absorption of the granules, which were believed to be caseous particles. Tuthill stated the belief that the unusual adventitial overgrowth noted in her case was an attempt to absorb these granules.

Ashby, Stewart and Watkin,[5] in the first of their 2 cases, mentioned only an area of thickened and opaque meninges, containing fibroblasts, lymphocytes and particles of yellow pigment, covering an area of cortical atrophy in the left cerebral hemisphere. The only abnormality noted in their second case was congestion of the pia-arachnoid. Green [6] stated that in his case the leptomeninges were thickened and contained scattered compound granular cells intermingled with large macrophages, without any elements of cellular reaction. No further description was given, and apparently no striking changes were noted. No mention of meningeal abnormality was made in the cases of Kressler and Aegerter,[7] de Lange [8] and Kny [9] or in the recent atypical cases of Strauss, Merliss and Reiser [10] and Josephy.[11]

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4. Tuthill, C. R.: Juvenile Amaurotic Idiocy: Marked Adventitial Growth Associated with Skeletal Malformations, Arch. Neurol. & Psychiat. **32**:198 (July) 1934.

5. Ashby, W. R.; Stewart, R. M., and Watkin, J. H.: Chondro-Osteo-Dystrophy of the Hurler Type (Gargoylism): A Pathological Study, Brain **60**: 149 (June) 1937.

6. Green, M. A.: Gargoylism (Lipochondrodystrophy), J. Neuropath. & Exper. Neurol. **7**:399 (Oct.) 1948.

7. Kressler, R. J., and Aegerter, E. E.: Hurler's Syndrome, J. Pediat. **12**: 579 (May) 1938.

8. de Lange, C.: Over dysostosis multiplex typus Hurler of Gargoylismus, Psychiat. en neurol. bl. **1-2**:2, 1942.

9. Kny, W.: Zur Kenntnis der Dysostosis multiplex Typ Pfaundler-Hurler, Ztschr. f. Kinderh. **63**:366, 1942.

10. Straus, R.; Merliss, R., and Reiser, R.: Gargoylism: Review of the Literature and Report of the Sixth Autopsied Case with Chemical Studies, Am. J. Clin. Path. **17**:671 (Sept.) 1947.

11. Josephy, H.: Lipoidosis of the Brain, J. Neuropath. & Exper. Neurol. **8**: 214 (April) 1949.

It is unlikely that the enormous thickening from proliferation of collagenous connective tissue and productive changes in the connective tissue of the pia-arachnoid noted in the present case were due to a reaction to the associated subdural hematoma. The pia-arachnoid nearest the hematoma showed the least change in connective tissue and only a very small amount of blood pigment. Nowhere else in the meninges was there any evidence of the accumulation of hemosiderin which would be expected if this reaction were a response to the severe hemorrhage on the right side or to previous hemorrhage on the left side.

The staining reactions leave no doubt that the major portion of the lipid in the meninges was a neutral fat. The consistent failure to obtain staining of all the cytoplasm leaves doubt as to the nature of the unstained portion of the cell. It is possible that several varieties of lipid, with different staining characteristics, are involved, or, as Green emphasized, that the process of cellular degeneration and lipid breakdown produces different products at different stages of the process.

Changes in tissues other than those of the nervous system proper have been described in cases with typical involvement of the neurons. In one brief report and in another (extensive) review of apparently the same case, Strauss [12] reported changes in the perichondrium, myocardium, blood vessels and heart valves in which the presence of large vacuolated cells had, in her opinion, stimulated the formation of collagenous fibers. Lipid storage was also noted in the reticuloendothelial system of the liver and spleen. It is evident that the extraneural alterations described by this investigator were very similar to those in my case. The accumulation of macrophages and the proliferation of connective tissue in the aorta and other arteries and in the endocardium especially are like those recorded by Strauss, and are perhaps even more extreme. Stimulation of collagenous connective tissue to such overgrowth, together with the formation of enormous numbers of lipid-laden macrophages, has never before been observed in the meninges and is peculiar to the present case. It clearly represents an extension of a generalized abnormality of the connective tissue to the pia-arachnoid rather than a localized process.

The changes observed in the neurons are, in general, similar to those of other investigators, with the exception of a few who described variant types, the exact nature of which is difficult to ascertain. A constant feature of all the cases is the normal, or very nearly normal, state of the cerebellum in a disease process affecting all other portions of the central nervous system. The cortex of the cerebral hemispheres is always involved, to varying degrees; but in general the regions of

12. Strauss, L.: A Case of Gargoylism, New York State J. Med. **47**:157 (Jan. 15) 1947; The Pathology of Gargoylism: Report of a Case and Review of the Literature, Am. J. Path. **24**:855 (July) 1948.

greatest pathologic change are the basal ganglia and the optic thalamus. There is considerable variation in the reports of investigators with regard to the degree of involvement in the various nuclear groups in the brain stem.

An excellent study of a typical case of lipochondrodystrophy, together with a recent review of the literature, was given by Green, who discussed the changes in the central nervous system in the child of whose brain Strauss made a general pathologic analysis.

Straus, Merliss and Reiser differed most strikingly from other investigators in their observations. They noted a slight variation in size of ganglion cells, but no ballooning. Some cells were large, and the cytoplasm contained a moderate amount of brown pigment. Such cells were most prominent in the basal ganglia and pons and were inconspicuous among the ganglion cells of the cerebral cortex. Staining reactions with sudan IV revealed a small amount of lipid in these large cells. In a normal brain stained in the same way as a control, they found as much lipid in similar areas as in the case under study. Chemical analysis revealed no increase in lipids of the central nervous system. These authors thus expressed doubt that a diagnosis of lipid storage disease was justifiable, but admitted that it is difficult to determine a small quantitative difference with accuracy.

In the case presented in this paper variations in the intensity of the pathologic process in different areas of the central nervous system were not pronounced, except that in general the larger cells were most affected and that, as other investigators have uniformly noted, the cerebellar changes were very slight. In this respect lipochondrodystrophy differs from amaurotic familial idiocy, in which alterations of the cerebellar structure are usually prominent.

The staining reactions of the abnormal lipid in the cortex varied considerably in reports by other investigators. It is hard to correlate my findings with those of others, though it would seem that the staining reactions in the cortex are similar to those of Kressler and Aegerter and Kny, who found that routine stains for fat were unsuccessful. As in the cases of de Lange, Kny and Green, no extracellular lipid was observed. The use of oil red O as a stain for lipids has not hitherto been reported in the study of lipochondrodystrophy, and its significance relative to other reported cases cannot adequately be ascertained. Again, as in the meninges, it is possible that the different affinity of the cytoplasm in the cortex for lipid stains is due to the different reactions of different lipids or the different reactions of the same lipid in varying stages of degeneration.

University Hospital.

CYTOPATHOLOGY OF THE BRAIN AND RETICULOENDOTHELIAL ORGANS IN ALLERGIC ENCEPHALITIS IN GUINEA PIGS

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AND
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MINNEAPOLIS

EPISODES of acute disseminated encephalomyelitis following infectious disease and a variety of immunization procedures have long been an enigma to pediatricians, neurologists and neuropathologists. Causative factors in these episodes may be placed in three categories, namely, virus invasion of the nerve tissue, allergic reaction to the infecting or inoculated agent and a specific autoallergic reaction to nerve tissue itself. Investigations during the past fifteen years have increased the cogency of the last hypothesis. Extensive studies with a variety of approaches have established beyond reasonable doubt that the nerve tissue, like other tissues of the body, responds violently to antigen-antibody reactions.[1] Miyagawa and Ishii,[2] Koritschoner and Schweinburg [3] and others showed that repeated injection of emulsions of normal homologous nerve tissue in experimental animals occasionally produces symptoms of disease of the central nervous system. Rivers, Sprunt and Berry [4] found that persistence with frequent injections of homologous or heterologous brain tissue over many months in experimental animals was rather regularly rewarded by the production of an acute diffuse

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This study was supported by a grant from the National Foundation for Infantile Paralysis, Inc.

1. Alexander, L., and Campbell, A. P. C.: Local Anaphylactic Lesions in the Brains of Guinea Pigs, Am. J. Path. **13**:229, 1937. Stevenson, L. D., and Alvord, E. C.: Allergy in the Nervous System, Am, J. Med. **3**:614, 1947.

2. Miyagawa, Y., and Ishii, S.: On the Influence of the Constituents of the Central Nerve Cells Parenterally Injected in the Living Organism, Jap. J. Exper. Med. **5**:331, 1923.

3. Koritschoner, R., and Schweinburg, F.: Klinische und experimentelle Beobachtungen über Lähmungen nach Wutschutzimpfung, Ztschr. f. Immunitätsforsch. u. exper. Therap. **42**:217, 1925.

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disseminated encephalomyelitis with clinical and pathologic characteristics similar to those of acute disseminated "leukoencephalitis" and acute episodes of multiple sclerosis in man. Rivers and Schwentker,[5] Schwentker and Rivers,[6] Ferraro and Jervis [7] and Kopeloff and Kopeloff [8] confirmed the earlier findings, extended the phenomenon to rabbits and demonstrated its association with the production of specific antibrain antibodies. Although these authors were aware of the possibility of introduction or activation of neurotropic virus infection, they were unable to demonstrate virus in the nervous system of their diseased animals and concluded that the experimental disease had an allergic basis.

Following the lead of Lewis and Loomis,[9] who showed that tuberculous guinea pigs produce more antibody response to nonspecific protein antigen than do nontuberculous guinea pigs, Freund and co-workers [10] developed adjuvants consisting of heat-killed tuberculous organisms and lipid substances which substantially increase the antibody response of an organism to a given antigen. In 1946, Morgan [11] and Kabat, Wolf and Bezer [12] simultaneously discovered that with the aid of Freund's adjuvants they could produce acute allergic disseminated encephalomyelitis regularly in monkeys after single or a few injections of either homologous or heterologous brain tissue. Morrison [13] and Freund and associates [14] extended this development to rabbits and

5. Rivers, T. M., and Schwentker, F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in the Monkey, J. Exper. Med. **61**: 689, 1935.

6. Schwentker, F. F., and Rivers, T. M.: The Antibody Response of Rabbits to Injections of Emulsions and Extracts of Homologous Brain, J. Exper. Med. **60**:559, 1934.

7. Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in the Monkey, Arch. Neurol. & Psychiat. **43**:195 (Feb.) 1940.

8. Kopeloff, L. M., and Kopeloff, N.: The Production of Anti-Brain Antibodies in the Monkey, J. Immunol. **48**:297, 1944.

9. Lewis, P. A., and Loomis, D.: Allergic Irritability: The Formation of Antisheep Hemolytic Amboceptor in the Normal and Tuberculous Guinea Pig, J. Exper. Med. **40**:503, 1924.

10. Freund, J., and McDermott, K.: Sensitization to Horse Serum by Means of Adjuvants, Proc. Soc. Exper. Biol. & Med. **49**:548, 1942. Freund, J., and Walter, A. W.: The Effect of Paraffin Oil, Lanolin-Like Substances and Killed Tubercle Bacilli on Immunization with Diphtheria Toxoid and Bact. Typhosum, J. Immunol. **48**:325, 1944.

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12. Kabat, E. A.; Wolf, A., and Bezer, A. E.: The Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injections of Heterologous and Homologous Brain Tissue with Adjuvants, Science **104**:362, 1946.

13. Morrison, L. R.: Disseminated Encephalomyelitis Experimentally Produced by the Use of Homologous Antigen, Arch. Neurol. & Psychiat. **58**:391 (Oct.) 1947.

14. Freund, J.; Stern, E. R., and Pisani, T. M.: Isoallergic Encephalomyelitis and Radiculitis in Guinea Pigs After One Injection of Brain and Mycobacterium in Water in Oil Emulsion, J. Immunol. **57**:179 (Oct.) 1947.

guinea pigs, respectively. Further studies with autoallergic brain disease in guinea pigs have demonstrated that in 50 to 90 per cent of the animals given single injections of homologous or heterologous brain tissue plus adjuvants there develops encephalomyelitis characterized clinically by spastic and flaccid paralyses, tremor, ataxia and encephalitis, with varying mortality.[15] The authors reported that remissions and exacerbations occur frequently. Pathologically, disseminated foci of perivascular infiltration and demyelination were observed to be characteristic. Recently, Koprowski and Jervis [16] have shown that complement-fixing antibodies against brain tissue accompany the development of allergic encephalomyelitis in guinea pigs.

Both collateral evidence of the operation of allergic mechanisms in human acute disseminated encephalomyelitis and multiple sclerosis [17] and common clinical and pathologic features of the experimental and human diseases [18] support the hypothesis that autoimmunization mechanisms may be playing an important role in the pathogenesis of disease of the human central nervous system.

During the same fifteen year period Burky [19]; Hecht, Sulzberger and Weil [20]; Schwentker and Comploier [21]; Cavelti and Cavelti [22]; Kerr and Cavelti,[23] and Heyman and Lund [24] showed similar mechanisms to

15. (*a*) Jervis, G. A., and Koprowski, H.: Experimental Allergic Encephalomyelitis, J. Neuropath. & Exper. Neurol. **7**:390, 1948. (*b*) Alvord, E. C.: Distribution and Nature of the "Antigen" Responsible for Experimental Meningoencephalomyelitis in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **67**:459, 1948.

16. Koprowski, H., and Jervis, G. A.: Further Studies in Experimental Allergic Encephalitis in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **69**:472, 1948.

17. Putnam, T. J.: Newer Concepts of Post-Infectious and Related Forms of Encephalitis, Bull. New York Acad. Med. **17**:337, 1941.

18. Ferraro, A.: Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain, Arch. Neurol. & Psychiat. **52**:443, 1944.

19. Burky, E. L.: Production in Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extractions by the Action of Staphylococcus Toxin, J. Allergy **5**:466, 1934.

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22. Cavelti, P. A., and Cavelti, E. A.: Studies on the Pathogenesis of Glomerulonephritis: III. Clinical and Pathological Aspects of the Experimental Glomerulonephritis Produced in Rats by Means of Auto-Antibodies, Arch. Path. **40**:158 (Sept.) 1945.

23. Kerr, W. J., and Cavelti, P. A.: New Immunological Aspects of the Pathogenesis of Glomerulonephritis and Rheumatic Fever, Tr. Am. A. Physicians **60**:264, 1947.

24. Heyman, W., and Lund, H. Z.: Lipemic Nephrosis in Rats, Science **108**: 448, 1948.

be operative in experimental diseases involving other organs and tissues, including the lens, skin, kidney, heart and connective tissue. These investigators produced experimental syndromes and pathologic processes comparable to those of acute glomerulonephritis, lipid nephrosis (nephrotic syndrome of unknown origin), endophthalmitis phaco-anaphylactica and lesions in the myocardium and endocardium similar to those of rheumatic activity in man by means of auto-antigen-antibody reactions. As is evident from this review, extensive work has been done in establishing in experimental animals a group of diseases on an autoallergic basis that simulate, both clinically and pathologically, disease states in man in which the pathogenic mechanisms have heretofore remained obscure.

It is the purpose of this paper to discuss in detail the cytogenesis of the various inflammatory cells in the lesions produced in the guinea pig by sensitization to homologous brain tissue. Especial attention will be directed toward the brain plasma cell because of its importance in the interpretation of the inflammatory mechanisms. In addition, the related and similar pathologic changes, hitherto overlooked, which may be found in the reticuloendothelial organs in this disease will be described and discussed.

The importance of the plasma cell in antibody production has been emphasized in a series of experimental papers, commencing with Kolouch's [25] demonstration of the concomitance of the rise of antibody titer with plasma cell formation in rabbits immunized to Streptococcus viridans. Many papers since have confirmed and extended this result, and the clinical observations on the association of hyperglobulinemia and plasmacytosis have been reviewed simultaneously with the experimental work in the papers of Fleischhacker [26]; Bjørneboe and Gormsen [27]; Fagraeus,[28] and Kolouch, Good and Campbell.[29] In the brain, the relation of plasmacytosis to the mechanisms of hypersensitivity have been shown by Good [30] in experimental inflammation of the brain and

25. Kolouch, F.: Origin of Bone Marrow Plasma Cell Associated with Allergic and Immune States in Rabbits, Proc. Soc. Exper. Biol. & Med. **39**:147, 1938.

26. Fleischhacker, H.: Ueber die Plasmazellen und das reticuloendotheliale System des Knochenmarkes: Beitrag zur Herkunft der Plasmaeiweisskörper, Deutsche Arch. f. klin. Med. **186**:506, 1940.

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28. Fagraeus, A.: Antibody Production in Relationship to the Development of Plasma Cells, Acta med. Scandinav. (supp. 9) **130**:1, 1948.

29. Kolouch, F.; Good, R. A., and Campbell, B.: The Reticulo-Endothelial Origin of the Bone Marrow Plasma Cell in Hypersensitive States, J. Lab. & Clin. Med. **32**:749, 1947.

30. Good, R. A.: Experimental Allergic Brain Inflammation: A Morphological Study, J. Neuropath. & Exper. Neurol., to be published.

discussed by Campbell [31] in relation to virus encephalitis. Local plasmacytosis has been found to be characteristic of allergic inflammation in other organs (Alessio,[32] in the liver; Klinge,[33] in joints; Goddard,[34] in connective tissue, and Good and Good,[35] in spleen and lymph node).

MATERIALS AND METHODS

Young adult guinea pigs were given subcutaneous injections of 3 cc. of a mixture of homologous brain tissue and Freund's adjuvants. The dose consisted of 90 mg. of guinea pig brain with 7.5 mg. of dried, heat-killed Mycobacterium butyricum in bayol-F® (liquid petrolatum U. S. P.) and falba® (ointment and absorption base of hydrous wool fat U. S. P.). Illness occurred in 85 per cent (17 of 20) of the animals so treated. The onset of symptoms was observed at thirteen to twenty-two days, with death in seventeen to forty-three days. The symptoms in this series have been described in another paper.[36] In addition to sections of tissues fixed in dilute solution of formaldehyde U. S. P. and stained with cresyl violet and erythrosin, imprints stained by the Romanowsky method were made for study of the finer cytologic detail. In making these sections, the cut surfaces of the brain and other organs were lightly imprinted on clean glass slides, and the imprints dried rapidly in air and stained with the Wright-Giemsa stain.

OBSERVATIONS

The general pathologic picture of the brains of the animals in this series resembled that described by Jervis and Koprowski.[15a] Scattered perivascular cuffing, as well as focal and diffuse infiltration, appeared throughout the central nervous system. The subependymal lesions and the lesions of the spinal cord seen by these authors were conspicuous (fig. 1 *A*) in our material. A wide variation in the maturity of the lesions was noted. Some were obviously young, showing a preponderance of polymorphonuclear leukocytes, together with occasional eosinophils and small lymphocytes. Other, more mature, lesions contained principally intermediate polyblasts, macrophages and plasma cells. Thus, the disease showed evidence of a continuing inception of lesions similar to, though more striking than, that described elsewhere for herpetic encephalitis in rabbits.[31]

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31. Campbell, B.: Early Plasma Cell Formation in Acute Herpetic Encephalitis, J. Neuropath. & Exper. Neurol. **8**:347, 1949.

32. Alessio, F.: Di alcune alterazioni istologiche ottenute nel fegato di conigli sensibilizzati colle iniezioni di antigene, Pathologica **21**:121, 1929.

33. Klinge, F.: Die Eiweissüberempfindlichkeit (Gewebsanaphylaxie) der Gelenke. Experimentelle pathologischanatomische Studie zur Pathogenese des Gelenkrheumatismus, Beitr. z. path. Anat. u. z. allg. Path. **83**:185, 1930.

34. Goddard, J. W.: Granuloma, Characteristic "Qualitative" Change in Focal Anaphylactic Inflammation, Am. J. Path. **23**:493, 1947.

35. Good, R. A., and Good, T. A.: Early Plasmacytosis of Spleen, Liver, Lymph Node and Connective Tissue, Anat. Rec. **103**:123, 1949.

36. Good, R. A.; Campbell, B., and Good, T. A.: Prophylactic and Therapeutic Effect of Para-Aminobenzoic Acid and Sodium Salicylate on Experimental Allergic Encephalomyelitis, Proc. Soc. Exper. Biol. & Med. **72**:341, 1949.

The cytodynamic development of the lesions as seen in the imprints revealed the evolution of macrophages from invasive lymphocytes, as demonstrated by Dougherty.[37] In the dense population of inflammatory cells of various species to be seen on the brain imprints, small lymphocytes, similar to those in the blood, were conspicuous. These cells had scanty cytoplasm and a dense, pachychromatic nucleus. The cells, seen infiltrating the organ, were grouped around the blood vessels, which they encased in dense cuffs, and, migrating outward, underwent evolution to the intermediate polyblast. This cell resembled in all detail the cells observed in connective tissue inflammation (Ekola[38]; Kolouch[39]; Townsend and Campbell[40]). The nucleus was expanded and frequently indented. The chromatin had assumed a stippled pattern against the background of heterochromatin. A more abundant cytoplasm, slightly basophilic, contained a few azure granules. Phagocytosis at this stage was seldom seen, but as the cell matured it took on the spongy cytoplasm characteristic of the macrophage (compound granular corpuscle, gitter cell, scavenger cell) and had incorporated in it detritus and erythrocytes. The nucleus lost its regular outline and became somewhat more pyknotic with age.

More conspicuous than the developmental sequence described in the preceding paragraph, and of particular interest in this disease, is the development of the plasma cell (fig. 1 *C*). A large number of the intermediate polyblasts acquired a more pronounced cytoplasmic basophilia and changed by gradual stages into the cell named by Good[30] the plasmacytic polyblast. These cells exhibited a condensation of the nuclear chromatin to form a coarse, checkerboard pattern. A *Hof,* or perinuclear halo, usually became clear at this stage. Physiologically, the cell was characterized by its failure to exhibit any phagocytosis. The cells became very numerous (up to 25 per cent on the imprints) and dominated the fields. Their subsequent history could be followed through progressive shrinkage of the cytoplasm and nucleus and the increased concentration of the nuclear chromatin into heavy plaques attached to the nuclear membrane. In sectioned material, the nuclei appeared wheel-like (*Radkern*), a pattern seen in plasma cells of all organs.

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37. Dougherty, T.: Studies on the Cytogenesis of the Microglia and Their Relation to the Cells of the Reticulo-Endothelial System, Am. J. Anat. **74**:61, 1944.

38. Ekola, M.: Reactions of Subcutaneous Tissue to Sodium Ricinoleate and Other Foreign Substances, Folia haemat. **43**:454, 1931.

39. Kolouch, F.: The Lymphocyte in Acute Inflammation, Am. J. Path. **15**: 413, 1939.

40. Townsend, W. A., and Campbell, B.: The Effects of Roentgen Rays on the Inflammatory Cells of the Mouse and Rabbit; Blood, to be published.

An impressive amount of glial activation was seen in the sections. By this is denoted the change in staining properties and morphology which occurred in the glia in inflammatory areas. As we have described elsewhere, the cells involved in these inflammatory changes were both the oligodendrocytes and the microgliocytes, the mesoglia of Robertson. This activation might occur in the absence of perivascular cuffing and give rise to the diffuse lesions so characteristic of the disease. Thickening of the nuclear membrane, increase in nuclear chromatin and formation of basophilic cytoplasm all contributed to the picture of glial activation. In areas so affected, the distinction between microglia and oligodendroglia, usually not difficult on the basis of nuclear pattern, became impossible, the reason being that the two cells converge, in activation, to a common cell type, comparable to, though morphologically distinguishable from, the intermediate polyblast. The cytoplasm was usually less copious and was a muddy blue in the stained imprints. The nucleus never "unfolded" to the same extent as did the nuclei of the lymphocyte. We have termed the mesoglial inflammatory cell the "activated glial" cell. In the lesions were seen all intermediate forms between these cells and the end forms of the two main inflammatory lines, the macrophage and the plasma cell. As mentioned before, the plasma cell line dominates the picture in allergic encephalitis, both in the cuffs of hematogenous inflammatory cells around the blood vessels and in the diffuse lesions, where the resident cells give rise to the inflammatory cell population.

The fate of the plasma cell of the brain in allergic encephalitis is apparently the same as that in experimental allergic inflammation and in herpetic encephalitis. A progressive increase in the basophilia of both nucleus and cytoplasm, together with pyknosis or shrinkage of all components, leads to dwarf remains, which are more prominent in the older lesions. Thus the mature plasmacyte, widely known as the Marshalkó cell, is but a stage in the history of a cell which has entered on the plasma cell cycle.

Most remarkable in these guinea pigs was the intense stimulation of the entire reticuloendothelial system. The concurrence of this type of bodily change with encephalitis was discussed previously in connection with herpetic encephalitis,[81] and the interpretation there made seems in all respects applicable to this condition. Particularly affected is the spleen, which is seen (fig. 1 *B*) to be tumorous and altered grossly, so that the distinction between red and white pulp is largely lost. Inspection of the sectioned and imprinted material revealed plasmacytosis of the most extreme degree. Every high power microscopic field consisted principally of the various stages of evolution of the plasma cell (fig. 1 *D*). The early stages were abundant and widely distributed, and the lines of development were easily studied.

Figure 2 illustrates the dynamics of plasmacytosis in the spleen, as seen in this material. Two lines of development are to be seen, as noted in similar material in the early papers of Bjørneboe and Gormsen,[27] Fagraeus[28] and Good.[30] The plasmacytic reticulum cell, described by Rohr[41] and substantiated in our previous studies on the bone marrow,[29] was present in considerable numbers, and transitional forms between it and the hematopoietic reticulum, as well as the large plasma cell, were to be seen as a continuous series. The plasmacytic reticulum

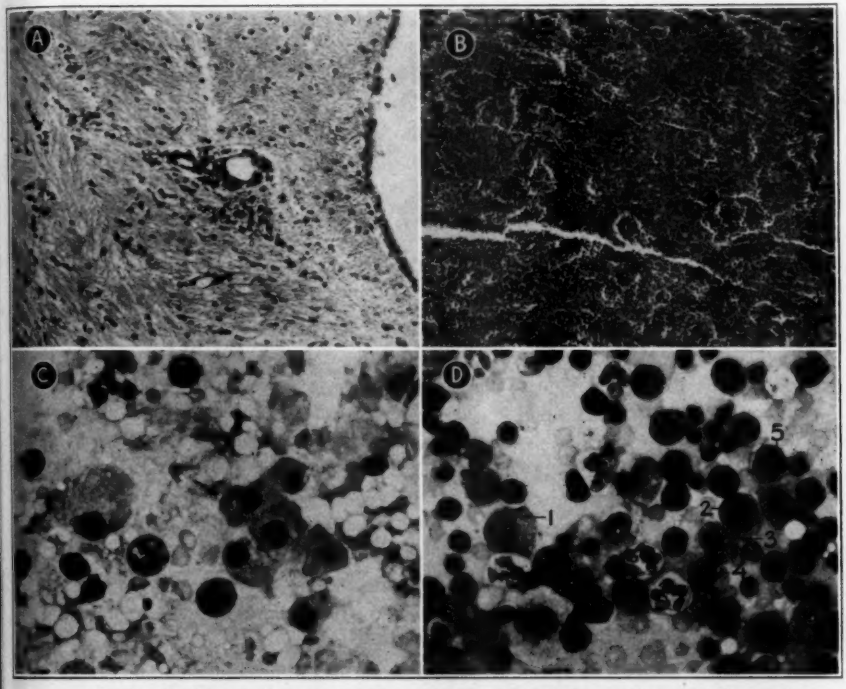

Fig. 1.—Pathologic changes in allergic encephalomyelitis. *A*, characteristic perivascular cuff surrounded by area of diffuse inflammation (× 107); *B*, spleen showing disruption of normal architecture (× 65); *C*, imprint of brain showing clump of young plasma cells (× 465); *D*, imprint of cells of spleen (× 465). Here, *1* is the plasmacytic reticulum cell; *2*, the lymphocytic plasma cell; *3*, the hematopoietic reticulum cell; *4*, the reticular plasma cell; *5*, the reticular lymphocyte.

cell may be characterized as a large diffuse cell, the nucleus of which shows an open chromatin pattern, similar to that of the primitive stem cell but differing in certain characteristics, which have been shown to

41. Rohr, K.: Blut- und Knochenmarksmorphologie der Agranulocytosen, Folia haemat. **55**:305, 1936.

indicate heightened protein metabolism. Especially noticeable are the chromocenters around the nucleoli, shown to consist principally of ribonucleotides.[42] In addition to the perinucleolar accumulation of chromatin, clumping of that material was observable throughout the nucleus. The changes were those seen in the formation of reticular lymphocytes but were more intense. Associated with the nucleus, which was not obviously plasmacytic, was a large cytoplasm with characteristic basophilia and a *Hof,* or perinuclear halo—plasmacytic features which were unmistakable. The subsequent development of this cell into the

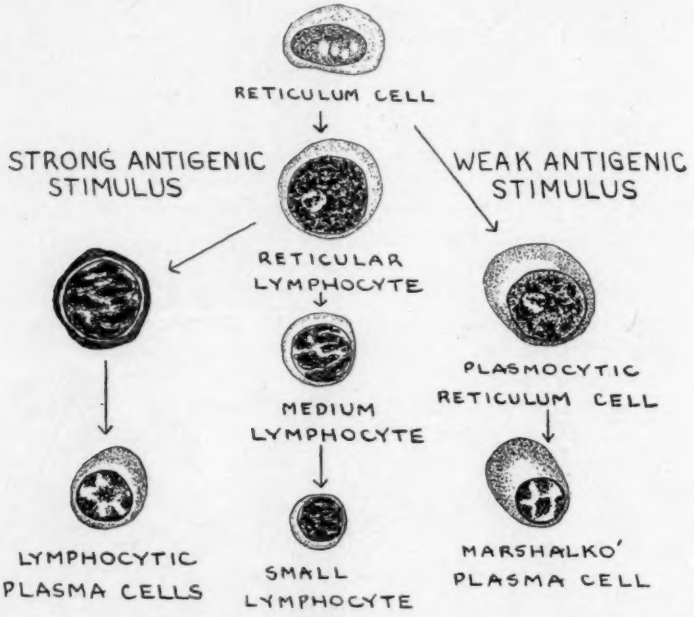

Fig. 2.—Diagram of splenic cells, showing evolution of the normal lymphocyte (center) and its alteration in the direction of the reticular plasma cell by weak antigenic stimulation (right). With strong antigenic stimulation, the cell line to the lymphocytic plasma cell (illustrated to the left) is added. Drawing by John B. Hyde.

large plasma cell, and eventually to the smaller Marshalkó form, was plain and has previously been described.[29]

More numerous by far was a plasmacytic line which develops from lymphocytes. These cells showed, in all stages, characteristics which differentiated them from the reticulum line just described, but the marks

42. Hydén, H.: Protein Metabolism in the Nerve Cell During Growth and Function, Acta physiol. Scandinav. (supp. 17) **6**:1, 1943.

by which plasma cells are identified were common to both. The large, immature form was a cell with a large nucleus containing coarse, plate-like aggregations of chromatin of distinctly plasma cell pattern. The cytoplasm was scant and only slightly eccentric. Nonetheless, it exhibited both the strong basophilia of all plasma cells and the distinct perinuclear halo. The cell is related to the reticular lymphocyte, and between them all intergrading forms may be observed. From it are derived, by the shrinkage process, which seems to be an aging phenomenon of all leukocytes, the smaller, more mature cell. At this stage the nuclear pattern is the same as that of the Marshalkó cell, but the cytoplasm is remarkable in its relatively small volume.

The latter type of plasma cell has been discussed at length by Moeschlin,[48] who stated that they are characteristic of the lymphoid tissue and are derived from a special plasmablast. As we report later in this paper, such cells are also to be found in the bone marrow. Moeschlin's plasmablast lies between our reticular lymphocyte and the early lymphocytic plasma cell. A comparison of these strongly activated guinea pigs with a series merely sensitized to egg white, and with a series of herpetic rabbits, has led us to interpret this dichotomy of the plasma cell line as a quantitative, rather than as a qualitative, phenomenon. When antigenic stimulation is not overwhelming the reticulum primarily is affected, and the lymphocytic plasma cells are rare. The reticulum apparently becomes submerged, numerically at least, in those animals in which the combination of tissue, bacterial antigen and oils makes the induced hypersensitivity the most violent sort. It would seem from our material that as the stimulus for plasma cell formation becomes stronger, cells further removed from the reticulum, such as the reticular lymphocyte cell, are aroused. This would give rise to a wider base of stem cells for the plasmacyte, and the final cells would not form two actual species but would represent extremes of a single broad evolutionary line. In our material, while the reticulum line of plasmacytosis could be seen with clarity, a sharp line was not observed to separate these cells from those, much more numerous, cells evolved from lymphocytes. The frequency of intermediate forms substantiates the view that the whole population of plasma cell precursors was widened to include the immature lymphocyte.

The cytologic picture of the bone marrow of these guinea pigs substantiated the suggestion here outlined that the two apparent lines of plasma cell derivation in the hematopoietic organs should be viewed as representing a widening of the base rather than as a true dichotomy. Our previous papers have described bone marrow which had received much less drastic stimulation than that in the present series. Thus

43. Moeschlin, S.: Die Herkunft der Blutplasma-Zellen bei der Hepatitis epidemica anhand von Milzpunktaten, Gasteroenterologia **71**:97, 1946.

the reticulum origin was apparent as the main feature. The great number of lymphocytic plasma cells in these animals was new to us. The cytopathologic picture was so like that of the spleen that a detailed account would be repetitious. It should be remarked only in passing that the preponderance of the lymphocytic plasma cell over the reticulum derivative in the bone marrow was far less extreme than that seen in the spleen.

COMMENT

This investigation has shown the concurrence of plasmacytosis and hypersensitivity to brain tissue plus adjuvants. In this it serves as further confirmation of the observations, cited earlier, that hyperglobulinemia is always accompanied with a rise in the number of plasmacytes. An extension of previous observations along this line is to be seen in the demonstration of local plasmacytosis in the organ the tissues of which were contained in the sensitizing antigen combination. Thus the organ-specific disease disseminated encephalomyelitis, resulting from exposure to brain antigens, produces the type of cellular reaction which experiments have previously linked with allergic disease.

The sequence of reactions which bring about this plasmacytosis is not entirely clear. Injection of a simple antigen into the blood stream will produce plasmacytosis in the reticuloendothelial system. Yet Good [30] found that within four days a significant plasma cell population did not appear in the cerebral cortex of rabbits when injections of egg white were made unless the animals were previously sensitized. From this, one might conclude that only after sensitization has occurred will the various multipotent connective tissue cells be stimulated to plasma cell formation. Bjørneboe and Gormsen [27] injected cowpox virus into rabbit skin and observed many plasma cells in the same four day interval, a reaction similar to that at Good's sites of injection in the previously sensitized animals. In this there may have been a quantitative difference in antigens. Virus antigen and bacterial antigen plus adjuvants may well show heightened effect on the tissues to the degree that only careful presensitization with weakly antigenic substances, like egg white, can give comparable results. That certain substances may have the properties of "natural antigens" through chemical relation to the body proteins of the host, however, must be considered a possible explanation for these findings.

The present concept of the pathologic mechanisms in encephalitis is based to a large degree on the consideration of the nerve tissues as consisting of a peculiar type of cell, the neurons, embedded in a matrix of somewhat related tissue, the glia, and quite unrelated to the various other organs in the body. The inadequacy of this concept has long been apparent, and the demonstration by del Rio Hortega and Pen-

field [44] of the reticuloendothelial nature of the microglia partly corrected this view. We concude that, whatever the germ layer derivation of the glia may be, the oligodendroglia, as well as the microglia, share the potentialities of most reticuloendothelial elements. It is unfortunate that no means of separating the true nerve cells from these actual or simulated connective tissue elements has been devised (or is likely to be), for it is impossible to prove the source of the antigen which is responsible for the specific reactivity of the brain to brain antigens. In consideration of this problem with relation to herpetic encephalitis, Campbell [21] pointed out that the virus invasion of the nerve cell could result in liberation of either or both of two antigens into the surrounding tissues. The virus itself might be the effective pathogenic agent as it passes from the cell to the surrounding milieu, or, again, the damaged nerve cells might equally well release antigenic substances. The work of Maculla [45] and of Cavelti and Cavelti [22] demonstrated that mesodermal organs, as well, may contribute organ antigens. Thus, the possibility that the supporting tissue of the brain, in addition to, or even to the exclusion of, the nerve tissue, acts in allergic encephalomyelitis cannot be ruled out.

The interpretation of virus encephalitis as depending on essential allergic mechanisms is strengthened by the presence of the identical cytopathologic features in a disease apparently purely allergic. It would seem that there is an equivalence between virus invasion and the presence of brain antigens (with adjuvants) in the circulation. In both situations a reaction of the tissue ensues which is of the same nature as that studied by Good in the experiments in which egg white and horse serum were injected into the cerebral cortex of previously sensitized animals. In the brain, however, this pathologic process is also characteristic of the chronic and recurrent types of encephalomyelitis, such as multiple sclerosis [46] and tertiary syphilis.[47] The key importance of antigen-antibody mechanisms in this type of disease process has led to an investigation of the results of salicylate therapy on allergic encephalitis in guinea pigs. The striking protection which adequate drug therapy affords in this disease is being described elsewhere.[36] Extension of this therapeutic approach to other encephalitides is being attempted on the basis of the pathologic considerations in this paper.

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44. del Rio Hortega, P., and Penfield, W., in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul Hoeber, 1932.

45. Maculla, E. S.: The Immunochemistry of Mouse Tissue Components: I. Comparative Antigenic Composition of Normal Mouse Tissue, Yale J. Biol. & Med. **20**:299, 1947.

46. Steiner, G.: Multiple und diffuse Sklerose, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, vol. 11, p. 289, 1930.

47. Michels, N. A., and Globus, J.: So-Called Small Round Cell Infiltration: II. Syphilis of the Central Nervous System, Arch. Path. **8**:371 (Sept.) 1929.

SUMMARY

A review of the pertinent literature reveals the importance of the plasma cell in the production of antibodies and as an index of allergic pathologic processes.

In a series of guinea pigs, made encephalitic by sensitization to homologous brain tissue plus adjuvants, the cytopathologic sequences are analyzed and the formation of plasma cells is described. The changes in the spleen and bone marrow are also detailed and compared with the changes in the same organs in simple hypersensitivity and in herpetic encephalitis. On the basis of this material, the interpretation is made that the reticulum and lymphocytic lines of plasmacytogenesis in the hematopoietic organs are essentially continuous and that strong antigenic stimulation causes a predominance of the latter type of cell. The allergic pathologic process described in this disease is proffered as a mechanism unifying virus encephalitis, chronic encephalitides and experimental allergic inflammation of the brain.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

AFFINITY OF SILVER LACTATE FOR ASTROCYTES. M. A. GEREBTZOFF, Acta neurol. et psychiat. Belg. **48**:607 (Dec.) 1948.

Gerebtzoff makes a preliminary report on a new technic for the impregnation of the macroglia. This consists in the use of a solution of silver lactate. The protoplasmic astrocytes and the cytoplasm of the fibrous astrocytes are stained a gray-violet, and the glial fibers appear black.

DEJONG, Ann Arbor, Mich.

Physiology and Biochemistry

EFFECTS OF HYPOPHYSECTOMY ON SERUM AND STORAGE IRON IN ADULT FEMALE RATS. R. C. CRAFTS and B. S. WALKER, Endocrinology **41**:340 (Nov.) 1947.

Crafts and Walker have evaluated the concentrations of serum and storage iron in normal, hypophysectomized and pair-fed (control) adult female rats. Hypophysectomized rats had decreased serum iron; this may have been due to decreased food intake, since the pair-fed controls showed a similar decrease. The liver, spleen, heart and kidneys in both the hypophysectomized rats and the pair-fed controls were decreased in size but had almost equally increased iron concentrations as compared with that for the normal rats. However, in the liver the iron concentration for the pair-fed controls was much higher than for either of the other animals. Iron concentration in muscle was similar for all the animals.

FRANKEL, Philadelphia.

PITUITARY AND CARBOHYDRATE METABOLISM OF THE BRAIN. M. REISS and D. S. REES, Endocrinology **41**:437 (Dec.) 1947.

Reiss and Rees found that hexokinase activity and anaerobic glycolysis were increased in portions of the gray matter of the brains of hypophysectomized rats. Oxygen consumption was unchanged after hypophysectomy.

FRANKEL, Philadelphia.

ADENYLPYROPHOSPHATASE IN BRAIN, LIVER, HEART, AND MUSCLE OF CHICK EMBRYOS AND HATCHED CHICKS. FLORENCE MOOG, J. Exper. Zool. **105**:209 (July) 1947.

The increase in adenylpyrophosphatase (apyrase) activity in organs of the developing chick was followed from twelve days of incubation until fourteen days after hatching. The methods and materials used were the same as those reported in a previous paper by Moog and Steinbach.

The enzyme content rises steadily in the brain, reaching its maximum about seven days after hatching. The first week after hatching is a period of great increase in vigor and alertness in the chick.

Apyrase activity of skeletal muscle reaches a peak at hatching and then declines slightly to the adult level. In cardiac muscle the apyrase attains its peak at sixteen days of incubation, declines at hatching and then decreases to the adult level.

Anoxemia may be the cause of the drop of enzyme activity in cardiac muscle at hatching. In the presence of added calcium, the apyrase activity of the liver rises sharply after hatching. Without added calcium, the activity remains almost unchanged throughout the period studied.

REID, New Brunswick, N. J.

THE SMALL-NERVE MOTOR SYSTEM TO SKELETAL MUSCLE. S. W. KUFFLER and R. W. GERARD, J. Neurophysiol. **10**: 383 (Nov.) 1947.

Kuffler and Gerard studied the electrical potentials of small nerve stimulation in the frog. The small nerves were studied by isolation of single fibers in the nerves, by differential block of large fibers and by specific reflex excitation. In contrast to the well known twitch response set up by excitation of a large vein fiber by a single stimulus, excitation of a small nerve fiber causes appreciable muscle shortening only on repetitive stimulation; and, while the shortening is local, considerable tension may be generated. Stimulation of a small nerve fiber sets up a local potential change at the neuromuscular junction. This potential spreads decrementially over several millimeters along the muscle fibers, and its general electrical properties are analogous to those of the curarized end plate potential of vertebrate muscles. Since this potential is set up by small nerve fibers, Kuffler and Gerard refer to it as the small fiber junction potential. The thresholds of the small nerve fibers are considerably higher than those of the large twitch-producing fibers. The small fibers are not of sympathetic origin. A single muscle fiber may be innervated by nerve fibers of both large and small diameters. The small nerve fiber system is active reflexly in animals immobilized by light ether or by decerebration.

FORSTER, Philadelphia.

THE ELECTRICAL ACTIVITY OF ISOLATED MAMMALIAN INTESTINES. N. AMBACHE, J. Physiol. **106**:139, 1947.

The electrical activity associated with pendulum movements was recorded from isolated preparations of mammalian intestine. Analysis of the records shows the existence of two distinct types of action potentials.

There is, first, a slow diphasic wave, the A wave, which precedes the onset of contraction by 0.5 to 1 second. This electrical disturbance may start at either end of the preparation and is conducted for distances far greater than the length of one muscle fiber.

With electrodes close together, there is also noted, after the A wave and during the contraction, a polyphasic response, the B activity, consisting of faster diphasic spikes, the duration of which appears to be independent of the distance between the electrodes. Both these responses persist after doses of nicotine which paralyze the ganglion cells.

When pendulum movements are inhibited by epinephrine or by an excess of calcium ions the B response disappears. Ambache believes that this polyphasic response consists of the action potential of asynchronous groups of muscle fibers. The A waves continue. The author suggests that these waves represent the discharge of a pacemaker in the intestine and that they may arise in the nerve net which was described by Cajal (1905).

THOMAS, Philadelphia.

EFFECTS OF ELECTRICAL STIMULATION OF THE CAROTID SINUS NERVE IN CATS. E. NEIL, C. R. M. REDWOOD and A. SCHWEITZER, J. Physiol. **107**:8P, 1948.

In cats anesthetized by the intravenous injection of chloralose (a compound of chloral hydrate and dextrose), 0.08 to 0.1 Gm. per kilogram of body weight, the

carotid sinus nerve was exposed and stimulated, using a square wave electronic stimulator. Stimulation of the carotid sinus nerve (containing afferent fibers from the carotid sinus and the carotid body) raises markedly the arterial blood pressure. The pressor effects persist after double vagotomy, destruction of the contralateral carotid sinus nerve, excision of the cervical sympathetic fibers, section of the glossopharyngeal nerve peripheral to the junction of the carotid sinus nerve, section of the stimulated carotid sinus nerve near its origin in the sinus and bilateral adrenalectomy. The effects are abolished by high spinal transection.

Stimulation of the carotid sinus nerve in the decerebrate cat or in cats under pentobarbital sodium® anesthesia (40 mg. per kilogram of body weight given intraperitoneally) produces the usual expected fall in arterial blood pressure. Subsequent intravenous injection of 0.05 Gm. of chloralose or more converts this depressor response into a marked pressor one. Apparently, chloralose masks the inhibitory effect of stimulation of the carotid sinus nerve on the vasomotor center in cats. The responses are independent of changes in respiratory activity.

THOMAS, Philadelphia.

LOCAL ELECTRIC CHANGES ASSOCIATED WITH REPETITIVE ACTION IN A NON-MEDULLATED AXON. A. L. HODGKIN, J. Physiol. **107**:165, 1948.

The variable nature of repetitive discharges is emphasized by a large body of experimental evidence. The present paper does not attempt to give a comprehensive theory of repetitive behavior; its object, rather, is to emphasize two points of general interest: (1) The long response times of axons of Carcinus are associated with the ability of these axons to give regular, low frequency discharges; and (2) both the response time and the repetition interval are determined by the development of subthreshold activity, which may be extremely slow under appropriate conditions. The experiments described suggest that the response time of a sense organ to a constant stimulus may be quite as important as its refractory period.

The initiation of repetitive discharges by constant currents was investigated by recording local electric changes from the stimulating electrode in isolated axons from Carcinus maenas.

On the basis of the types of repetition encountered, the axons were classified as follows: (1) axons which are capable of responding over a wide range of frequencies (5 to 150 per second); (2) axons with a pronounced supernormal phase, this class giving a train of impulses of a frequency of 75 to 150 per second which was relatively insensitive to the strength of the applied current, and (3) axons with a high threshold and a low safety factor, which either failed to repeat or succeeded only if the current strength was much greater than rheobase.

THOMAS, Philadelphia.

Neuropathology

INCLUSION BODIES ASSOCIATED WITH DESTRUCTION OF NERVE CELLS IN SCRUB TYPHUS, PSYCHOSES, AND MULTIPLE SCLEROSIS. JAMES W. PAPEZ, J. Nerv. & Ment. Dis. **108**:431 (Nov.) 1948.

The cases studied appeared to be associated with specific types of inclusion bodies and a destructive pathologic process in which nuclear reactions and cytolysis were outstanding features. In 2 cases of scrub typhus some nerve cells showed small, elongated or rod-shaped bodies in the cytoplasm of microglial nodules or of the microglial cells of endovascular cuffs. In 2 cases of anterior poliomyelitis the cytoplasmic inclusions were found in nodules of proliferating microglial cells around blood vessels of the spinal cord.

In 29 biopsy specimens taken during frontal lobotomy in schizophrenic patients, three stages of cytolysis with associated inclusion bodies were demonstrated. In the early stage, elongated or rod-shaped inclusions were present; a more advanced stage was characterized by vesicular nuclei and severe cytolysis in the parts occupied by the inclusions; the last stage was represented by nuclei almost stripped of cytoplasm, dentrites and axons.

In postmortem material from older patients with chronic psychoses the cytoplasmic destruction was delayed, the inclusion bodies were of large size and cells of the cortex, thalamus and hippocampus were affected. The patients with hallucinations showed marked organic disease of the cells of the thalamic nuclei and actual destruction of cells in the medial and lateral geniculate bodies and of other nuclear masses. Perivascular cuffs with degeneration products of inclusion bodies were numerous.

In 8 cases of multiple sclerosis the most pronounced changes were in the spinal cord, where the small reflex cells and the sensory cells of the dorsal horn were most often destroyed. The large cells of the motor horns and the cells of Clarke's column were seldom broken down, even when heavily filled with inclusions. Perivascular cuffs with degenerating inclusions were usual. FARMER, Philadelphia.

NEUROBLASTOMAS. A. THO, Nord. med. **40**:2211 (Nov. 26) 1948.

In the 3 cases of neuroblastoma reported in children aged between 1 and 6 years with typical localization in the adrenal medulla, the clinical picture was dominated by cranial metastases. Tumor cells demonstrated in the bone marrow and roentgenologically established metastases to the bone system facilitated the diagnosis. Death from cachexia occurred after two and a half to six months. Tho says that in differential diagnosis myeloblastic leukemia is first to be considered; the clinical picture together with the sternal puncture and roentgenologic picture as a rule clarifies the situation. In 2 of the cases signs of lively blood regeneration with high reticulocyte count were found; in leukemia there is most often little tendency to blood regeneration. Wilms's tumor seldom leads to bone metastases; urograms, often positive with this tumor, are usually negative with neuroblastoma. Ewing's tumor is rare in patients under 4 years of age. Metastases generally give the first and characteristic symptoms of neuroblastoma. The tumors are radiosensitive. In Farber's series of 40 patients, 10 are living after three to eight years, and Farber would revise the earlier hopeless view of the prognosis. Irradiation cannot hinder the development of metastases, which may be latent several years, but they also are radiosensitive. Irradiation of skeletal metastases has not prevented recurrence.

J. A. M. A.

Psychiatry and Psychopathology

ON SOME PSYCHODYNAMICS OF MASOCHISM. BERNHARD BERLINER, Psychoanalyt. Quart. **16**:459 (Oct.) 1947.

Berliner had previously suggested the theory that it is not the sadism of the masochist himself that is turned upon his ego, but the sadism of another person, a love object. The subject accepts the sadism of the love object for libidinal reasons and turns it upon himself by way of introjection, identification and superego formation. It is thus a disturbance of interpersonal relations, a pathologic way of loving.

Berliner states that the normal adult, experiencing an absence of love, hates in return and gives up the love object; but the dependent child, in order not to lose the vitally needed love object, submits and accepts the suffering which the object imposes as if it were love, and is not conscious of the difference. The child introjects the pain-giving object because of an oral need for its love. Simultaneously, the child represses any hostile reaction against the loved object because that also would cause its loss. The child does not love suffering or ill treatment, but, because he loves the person who gives it, he libidinizes the ill treatment. Masochism, then, is the hate or the sadism of the object reflected in the libido of the subject. This original situation is kept alive by the superego through transference to any suitable person or set of circumstances in later life.

The author states that most masochistic persons retain enough normal aggressiveness not to leave the struggle for self preservation entirely to the denial and libidinization of suffering. They develop aggressive attitudes against the frustrating love object and its repetitions in transference. This masochistic aggressiveness appears in two ways. First, it is an intensified bid for affection, and, second, masochistic aggressiveness is a more intense form of the magic gesture characterized by the idea "You will be sorry."

The author is careful to distinguish moral masochism from compulsive neurosis, with which it is often confused. He points out that masochism develops from oral erotism and is the libidinal reaction to another person's sadism, while compulsion neurosis stems from anal erotism and from the subject's own sadism and the fear of its consequences, although masochistic motivations often assist in this development.

WERMUTH, Philadelphia.

FEMININE SIGNIFICANCE OF THE NOSE. L. J. SAUL, Psychoanalyt. Quart. **17**:51 (Jan.) 1948.

Saul points out the bisexual nature of symbols and of psychogenic organic symptoms. He describes three dreams of a man whose central problem was latent homosexuality. These dreams show the use of the nose as representing a vagina and a connection of both these organs with the anus. The author states that this concept is in accord with the well known physiologic relationship of nose and genital organs, and presumably reflects this relationship in the psychologic sphere. The unconscious passive feminine wishes of the patient described by the author apparently played a role in his pruritus ani, his habit of picking his nose and possibly his sinusitis.

WERMUTH, Philadelphia.

ELECTRIC SHOCK AS A DIAGNOSTIC AID IN SCHIZOPHRENIA. L. HALPERN, Monatsschr. f. Psychiat. u. Neurol. **118**:61 (July) 1949.

Halpern cites 4 cases of young adults whose clinical presenting symptoms were depression, indifference and inhibition in action and speech. In 2 cases the diagnosis was endogenous depression; in the third case, melancholia of cyclic nature, and in the fourth the patient had had a previous schizophrenic episode but at the time of the acute episode was apparently depressed. After the third to the fifth electric shock treatment the patients became restless, aggressive, confused, delusional and hallucinated and presented the picture of an acute schizophrenic episode. The author considers the shock treatment responsible for the emergence of the underlying schizophrenic structure, which had been masked by the depressive façade.

PISETSKY, New York.

CONSTITUTIONAL AND EMOTIONAL FACTORS IN ETIOLOGY OF HYPERTENSIVE VASCULAR DISEASE. J. Groen and J. H. REISEL, Nederl. tijdschr. v. geneesk. **92**:3705 (Nov. 13) 1948.

According to Groen and Reisel, it is well known that the blood pressure of normal persons fluctuates considerably under the influence of emotions, and in patients with hypertensive vascular disease this seems to be so to an even greater extent. Frequently patients themselves ascribe an intensification of their hypertension to some emotional annoyance. The authors tried to determine whether the character structure of these patients is such that they are predisposed to emotional conflicts and whether the onset or exacerbation of the hypertension was preceded by an emotional upset. They obtained their data from 50 patients with hypertensive vascular disease, whose ages varied from 18 to 60. They found that these patients are usually active, hard-working persons with a tendency to perfectionism. They are inclined to lead and to dominate. They are not satisfied with themselves, and, while outwardly they may appear self assured, inwardly they are not. Many make great efforts to adjust themselves to their surroundings; they have a great need to be loved and appreciated. One of the most fundamental characteristics of these patients is a strong destructive aggressiveness, and this, combined with the need for love and appreciation, makes for chronic conflict situations.

J. A. M. A.

Meninges and Blood Vessels

TWO CASES OF TEMPORAL ARTERITIS: ONE WITH ANGINA OF EFFORT. L. COLE, Brit. Heart J. **10**:26 (Jan.) 1948.

The age of onset in Cole's 3 patients was between 65 and 72, and the symptoms and signs produced by involvement of the temporal arteries ran a course lasting from four to six months. All 3 patients showed evidence of arteriosclerosis in the radial and brachial arteries, and 2 died suddenly of cardiovascular accidents. The key to the diagnosis was severe headaches, leading to the discovery of involvement of the temporal arteries. More cases should be published in order that the condition may be widely recognized and more may be learned about its protean manifestations. At present the general verdict is that the prognosis is good so far as the local condition in the temporal arteries is concerned, for this tends to clear up in about a year. It is not yet so clear how far extension of the process to more vital arteries may be responsible for deaths such as occurred in these patients, and follow-up observation of more cases is needed. J. A. M. A.

HISTOPATHOLOGY OF ATYPICAL LYMPHOCYTIC VIRUS MENINGITIS. VON A. JUBA and J. PRIEVARA, Confinia neurol. **9**:381, 1949.

Juba and Prievara describe the histopathologic changes in 2 cases of "atypical lymphocytic virus meningitis." In both cases signs of meningeal irritation were associated with bulbar and spinal weakness. The cerebrospinal fluid findings are not given in the first case. In the second there were 142 lymphocytes per 3 cc. in the spinal fluid and 62 per 3 cc. in the cisternal fluid. Although the anterior horns showed the chief alterations, namely, tissue infiltration, cell destruction and perivascular lymphocytic accumulations, there was some involvement of the posterior horns as well. The inferior olivary nuclei were also affected, and there were extensive subarachnoid hemorrhages. On the basis of this histopathologic evidence, the authors argue that in these cases the condition could not be poliomyelitis.

FOLEY, Boston.

Diseases of the Brain

CHARACTER OF NYSTAGMUS INDUCED BY AMYTAL IN CHRONIC ALCOHOLICS. M. B. BENDER and C. A. BROWN, Am. J. Ophth. **31**:825 (July) 1948.

While studying the effect of barbiturates on ocular movements, Bender and Brown observed that in chronic alcohol addicts intravenous injection of amytal sodium® (sodium isoamylethylbarbiturate) produced fine, shimmering nystagmus, instead of the coarse, slow nystagmoid movement which is generally seen with barbiturate intoxication in persons not addicted to alcohol. Comparative tests were made on 15 alcohol addicts and 15 controls not addicted to alcohol. A 5 per cent solution of amytal sodium® was injected into the antecubital vein at a rate not exceeding 0.1 Gm., or 2 cc., per minute. The total dose was never more than 0.5 Gm., or 10 cc. During these tests the patient was instructed to fix his gaze on an object away from the central visual axis. In the control subjects injection of amytal sodium® generally produced ocular responses of two types: (1) wide, slow irregular oscillations, in which the eye drifted slowly toward the midline from a point of fixation and return to the original position with a flick, and (2) coarse, slow rhythmic nystagmus. All patients addicted to alcohol showed fine, shimmering nystagmus. In 1 patient the type of nystagmus helped the discovery that the patient had been an alcoholic addict, which he had denied at first. It appears that if alcohol is imbibed over a long period it alters the function of the nervous system. The fine, rapid nystagmus is found even months after the patient has stopped drinking. This suggests that alcohol produces a more or less permanent change in function of the nervous system. J. A. M. A.

INTRACRANIAL AND CERVICAL TRAP LIGATION OF THE CAROTID ARTERY COMPLICATED BY BLINDNESS IN THE HOMOLATERAL EYE. DONALD MATSON and BARNES WOODHALL, J. Neurosurgery **5**:567 (Nov.) 1948.

The loss of vision in the homolateral eye after ligation of the carotid artery, either intracranially or extracranially or both, has rarely been reported. The reason for this lies in the rich anastomosis of the ophthalmic artery with the branches of the external carotid artery in the orbit, as well as free anastomosis of branches of the two external carotid arteries across the midline of the face.

The case reported is that of a Negro woman aged 26 who had had two attacks of severe pain behind her left eye and, after the last episode, had noted paralysis of the third nerve on the same side. An arteriogram of the left internal carotid artery showed a saccular aneurysm at the origin of the posterior communicating artery from the internal carotid artery. The left common and internal carotid arteries were ligated in the neck, and a silver clip was placed just proximal to the bifurcation of the anterior and middle cerebral arteries. One month after operation the patient was free of headache but was completely blind in the left eye, a condition which she had noted since she had regained consciousness after operation. She had almost complete recovery of the third nerve paralysis. The left optic disk was very pale, and only consensual pupillary action was present in the left eye. Six months later the findings were the same, with an increase in the atrophy of the left disk.

The authors give two possible causes of this blindness: (1) production of thrombosis of the ophthalmic artery extending from the trapped portion of the internal carotid artery before adequate collateral circulation from the opposite external carotid artery could be established and (2) the presence of an anomalous blood supply.

They suggest that it is unwise to ligate the common carotid artery in the neck when trying to trap an aneurysm located on the intracranial portion of the internal carotid artery.

TOZER, Philadelphia.

CYSTIC PITUITARY ADENOMATA. J. E. PATERSON, J. Neurol., Neurosurg. & Psychiat. **11**:280 (Nov.) 1948.

Among pituitary tumors, the incidence of cystic adenomas has been reported as varying from 17 to 43 per cent. Paterson would restrict the term cystic to tumors from which the operator can aspirate an appreciable amount of fluid. In the present series, he found such tumors in 10 of 49, or 20 per cent, of cases of pituitary adenomas. An average of 10 cc. was noted in the 7 cases in which the fluid was measured. The cyst content was either a clear yellow fluid, tending to spontaneous clotting, or a dark, opaque fluid with the color of altered blood and cholesterol crystals. Biopsy specimens in 9 of the 10 cases disclosed histologic features similar to those of the solid type of tumor. Eight of the tumors were classified as chromophobic and 1 as acidophil adenoma. In the tenth case the cyst contained thyroid-like vesicles characteristic of the pars intermedia of the pituitary. There was no evidence of a greater tendency to recurrence of the cystic growths, as suggested in the literature. Recovery of vision and expansion of fields tended to be more rapid and complete in the cases of the cystic type. This may be due to the rapid development of the cysts and to short duration of pressure on the chiasma, so that irreversible damage to the chiasm is relatively less. The clear yellow fluid of some cysts is probably due to altered permeability of the blood vessel walls, allowing albumin, globulin and fibrinogen to escape into the tumor. The dark color of the fluid in others is due to rupture of blood vessels or to high intracapsular and consequently high venous pressure, allowing for escape of blood. The author includes a case report in which operation on a cystic tumor was followed by improvement of vision. Later, two recurrences took place, which were treated with roentgen radiation, with ultimate fatal hypothalamic atrophy.

N. MALAMUD, San Francisco.

NEUROLOGIC SEQUELAE OF FAMILIAL HEMOLYTIC DISEASE; INTEGRITY OF HEPATIC PARENCHYMA VERIFIED SEVEN YEARS AFTER ONSET OF NERVOUS SYMPTOMS. R. TURPIN and H. DUCHÊNE, Nourrisson **36**:189 (Nov.-Dec.) 1948.

Turpin and Duchêne report on a boy aged 6½ years who was admitted to the hospital for a choreoathetoid syndrome with extrapyramidal symptoms of Little's disease and cerebellar disturbances. Involuntary movements and disturbance of speech made the utilization of Binet's test difficult, but the mental capacity could be considered normal. Two weeks before the admission of the patient his mother was delivered of her second child, a boy who had kernicterus for one month. Examination of the blood of the parents and of the newborn baby demonstrated isoimmunization of the mother in response to having been pregnant with an Rh-positive fetus. The history of the older boy revealed that he had presented icterus for the first days after birth, difficulties in growth and nutrition, insomnia and convulsions and that at the age of 3 he could not walk and could pronounce only a few words and those with difficulty. A biopsy of the liver performed on the older boy at the time his younger brother presented icterus demonstrated that structure and function of the cells of the parenchyma were normal. The younger boy, now aged 2, cannot pronounce more than the few words he had been able to

pronounce when he was 1 year old; he cannot walk and he can assume an erect position only with support. The younger brother thus presents neurologic disturbances similar to those of his elder brother. In both patients these disturbances may be considered sequelae of kernicterus. From the case of the older patient, and from others cited in the literature, it is concluded that the association of kernicterus and cirrhosis is an exception which seems to be the result of a local effect of the hemolytic process. The disturbance must be distinguished from the hepatolenticular degeneration of Wilson's disease, in which the association of the hepatic and neurologic disturbances may result either from a linkage or from the spread to the liver of neurologic lesions by which certain metabolic centers are affected.

J. A. M. A.

Diseases of the Spinal Cord

PERNICIOUS ANEMIA WITH CHANGES IN THE SPINAL CORD IN A YOUTH WITH FAMILIAL TENDENCY. H. M. CANELAS, M. ABU JAMRA and ORLANDO AIDAR, Arq. neuro-psiquiat., São Paulo **7**:57 (March) 1949.

A mentally retarded Brazilian (white) aged 20 had experienced insidious onset of weakness in the lower extremities and paresthesias in all four limbs for two years. Physical examination showed nothing significant, but four months later, after a slight rise in temperature, there suddenly developed complete paraplegia with a picture of transverse myelitis at the third thoracic level. He had flaccid paraplegia with absence of reflexes in the lower limbs and of plantar responses. There was no evidence of block. The total protein was 20 mg. per hundred cubic centimeters; the Wassermann reaction of the spinal fluid was negative. The pictures of the blood and bone marrow were those of pernicious anemia. The patient died of bronchopneumonia four months after onset. Autopsy showed typical combined degeneration of the cord. The authors emphasize the patient's youth and the familial tendency of the disease.

N. SAVITSKY, New York.

COMBINED SYSTEM TABES: REPORT OF A CASE. FRANCISCO I. CURCIO, Prensa méd. argent. **36**:1123 (June 17) 1949.

Curcio reports the case of an Argentinian, aged 34, who had a primary syphilitic lesion at the age of 21. In 1943 he was hospitalized for investigation of bloody diarrhea, which was thought to be due to a parasitic infection. While he was in the hospital, weakness of the lower limbs was noted. In 1944 he began to complain of severe pain in the lower limbs. Sexual impotence appeared at that time. In 1945, in addition to the recurrent sharp pain in the lower limbs, he complained of numbness and other paresthesias. In November 1946 he was admitted to the hospital, where examination revealed atrophy with hypotonia of the muscles in all four limbs, and weakness of various muscles in the upper and lower limbs. There were no fibrillations. The knee jerks and the right ankle jerk could not be elicited. The left knee jerk was diminished. The abdominal reflexes were present on both sides. There was an equivocal Babinski sign on the right. Position sense was impaired in the feet, and vibration sense was diminished in the lower limbs. There were sensory changes in the lower limbs, suggesting root involvement. The serologic reactions of the blood and spinal fluid were positive. Intramuscular injection of 4,000,000 units of penicillin over a period of seventeen days had no appreciable effect. The author considers the case one of parenchymatous involvement of the posterior columns and pyramidal tracts.

N. SAVITSKY, New York.

CASE OF PAGET'S DISEASE (OSTEITIS DEFORMANS) WITH SYMPTOMS OF COMPRESSION OF THE CORD TREATED SURGICALLY: REPORT OF A CASE. GUNNAR WIBERG, Rev. Asoc. méd. argent. **62**:740 (Dec. 15) 1948.

Wiberg reports the case of a man aged 54 who had lumbago in 1906 and sciatica on the left side in 1929, the latter necessitating his remaining in bed for several weeks. During 1933 and 1934 he had pain in the lower limbs posteriorly with irradiation to the calves. Walking caused exacerbations of pain. Early in 1944 there appeared weakness in the legs and, toward the middle of the same year, paresthesias. He was admitted to the hospital in 1945, where roentgenographic changes were noted in the first to the fourth lumbar vertebrae, due to Paget's disease. There were similar changes in the pelvis. A roentgenogram of the skull showed nothing remarkable. Pneumomyelographic studies with oxygen showed a block at the first lumbar segment. Weakness of the flexors of the knees and paralysis of the extensors of the feet and toes were found. The knee jerks and the left ankle jerk were absent. The Babinski sign was not elicited. Extensive sensory changes were noted in the legs. A laminectomy was followed by definite improvement. The author collected 16 other cases in which operation was performed for compression of the cord due to Paget's disease. Most of the lesions were in the thoracic region, with some at the upper lumbar level, as in this case.

N. SAVITSKY, New York.

BILATERAL POST-TRAUMATIC PARALYSIS OF THE EXTERNAL RECTUS. G. HOFFMANN and L. ECTORS, Acta neurol. et. psychiat. Belg. **48**:421 (Sept.) 1948.

Hoffmann and Ectors report 2 cases of bilateral post-traumatic paralysis of the external rectus. They state that the presence of such bilateral paralysis in the absence of other neurologic signs or of skull fracture makes it logical to assume a mechanism of simple stretching of the nerves by hyperextension of the head. The paralysis is usually transitory, and one can anticipate complete return of motor function within one year.

DEJONG, Ann Arbor, Mich.

Peripheral and Cranial Nerves

PROGNOSTIC SIGNIFICANCE OF "GUILLAIN-BARRÉ SYNDROME." M. HAND and M. RUDOY, Ann. Int. Med. **29**:91 (July) 1948.

Hand and Rudoy report 11 cases of polyneuritis observed in American soldiers abroad between the ages of 20 and 41, 10 of whom had a definite history of pharyngitis, which preceded the onset of neurologic disturbance by three to six weeks. In all cases the condition was characterized by diminution of motor power, reflexes and sensibility in the extremities. Difficulties in accommodation and swallowing were common at the onset, and urinary disturbances were noted. Elevation of the total protein content of the spinal fluid without increase of cells was present in every case. In 6 of the 11 cases an exacerbation of symptoms occurred after partial recovery. Two cases of polyneuritis in American civilians in New York, occurring one month after a severe sore throat in 1 case and two months after pyodermia in the other, had a similar course to that of the 11 soldiers. Five additional cases of polyneuritis in German prisoners of war are reported in which the throat smears revealed the presence of diphtheria bacilli. In these cases the total protein of the spinal fluid was normal or only slightly elevated. Similarly, in 4 additional German prisoners with polyneuritis associated with

extraordinary ingestion of sulfonamide drugs over a long period there was no elevation of the total protein in the spinal fluid. Fever was not present in any of the cases in association with the neurologic disability but was present in rare instances at the time of the throat infection, weeks before. Spontaneous pains or burning sensations occurred, but were not common in this series. Treatment consisted of bed rest, physical therapy from the onset of motor weakness, use of thiamine chloride, 300 mg. daily, and a diet high in vitamins. Activity was permitted to the extent of the patient's capability. All the patients recovered, and none was left with disabling residua. The minimal febrile reaction, symmetry of limb involvement and occurrence of subjective and objective sensory changes differentiate the syndrome clinically from anterior poliomyelitis. The spinal fluid findings offer definite diagnostic evidence. Postdiphtheritic neuritis closely resembles the Guillain-Barré syndrome, as has been shown in the 5 cases of polyneuritis in the German prisoners with diphtheria bacilli. Differentiation depends on demonstration of diphtheria bacilli and on the relatively slight elevation of total protein in the spinal fluid. Etiologic relation to throat infections, such as tonsillitis, exudative pharyngitis of streptococcic or diphtheritic origin and pyemia, is apparent. Sulfonamde drugs used in treatment of these primary infectious conditions may on occasion constitute the etiologic agents in the neurologic syndrome.

J. A. M. A.

MENINGITIS DUE TO PSEUDOMONAS PYOCYANEA: REPORT OF THREE CASES TREATED SUCCESSFULLY WITH STREPTOMYCIN AND SULFADIAZINE. L. WEINSTEIN and T. S. PERRIN, Ann. Int. Med. **29**:103 (July) 1948.

Weinstein and Perrin successfully treated 2 women aged 33 and 58, respectively, and a boy aged 16, who had primary meningitis due to Pseudomonas aeruginosa with intrathecal and intramuscular injections of streptomycin combined with sulfadiazine or sulfamerazine. In all the patients infection of the meninges occurred during the course of spinal anesthesia. The source of the organism could not be determined. The strains of Ps. aeruginosa responsible for the infection were sensitive to between 7.8 and 30 units of streptomycin per cubic centimeter and did not become resistant to the drug during treatment. Penicillin injected intrathecally was given a brief trial but was singularly ineffective. The sulfonamides, used alone, also failed to control the meningeal infection, although temporary moderate improvement was produced by large doses. Streptomycin is indispensable in successful treatment of primary meningitis due to Ps. aeruginosa. When combined with sulfadiazine or sulfamerazine, it appears to be the treatment of choice. The total dose of streptomycin administered intrathecally varied from 1.8 to 8.1 Gm., and that given intramuscularly, from 36.5 to 227 Gm. Two patients had from one to four relapses of the meningeal infection when treatment was stopped. These recurrences were accompanied with the presence of a variable number of red blood cells and occasionally with xanthochromia in the spinal fluid. Deafness occurred as a complication in all the patients, and 1 of them showed severe labyrinthine disturbance with complete loss of vestibular function. There was improvement in hearing in all the patients after discontinuation of the antibiotic therapy.

J. A. M. A.

ERB'S PALSY, B. WOLMAN, Arch. Dis. Childhood, **23**:129 (June) 1948.

The term Erb's palsy is applied to that type of birth palsy in which the paralysis, or paresis, is confined to muscles supplied by the fifth and sixth cervical nerves. The deltoid, supraspinatus, infraspinatus, teres minor, biceps, brachialis, brachi-

oradialis and supinator muscles are usually involved in cases of severe disease, whereas in cases of mild disease only some of these muscles are involved. Wolman reviewed the cases seen at the outpatients' department of a busy provincial teaching hospital during the last twenty-one years. Actually 125 persons with Erb's palsy presented themselves during that time, but the author has been successful in tracing and interviewing only 37 of this group. Injury at birth to the supraclavicular portion of the brachial plexus is the accepted cause of the condition. Skilled obstetric technic in delivery, particularly in the use of forceps, is the main factor in avoiding this paralysis. Large babies are more likely to be injured. A large child in a primigravida needs special care with the delivery of the head and arms. Treatment must be carried out from birth. Infants treated within the first month do well, and results are 100 per cent successful. If treatment is delayed, contractures causing impaired function of the shoulder and elbow will develop quickly. The treatment consists of adequate splintage, associated with massage, together with exercises for older children. J. A. M. A.

BRACHIAL NEURITIS DUE TO CERVICAL INTERVERTEBRAL DISK LESIONS. E. WALKER, Georgia M. A. J. **38**:1 (Jan.) 1949.

According to Walker, rupture or herniation of a cervical intervertebral disk is the usual cause of pain, which extends from the lower cervical portion of the spine into the upper extremity. The clinical picture is that of so-called brachial neuritis, with pain involving one of the lower cervical nerve roots. The patient usually complains of pain over the suprascapular region, often radiating into the shoulder region and distally down the arm. If the nerve root is sufficiently damaged, there may be reflex or sensory changes, and these neurologic findings will be of considerable importance in determining which nerve root is involved and which disk is ruptured. Roentgenologic studies of the cervical part of the spine will aid in the diagnosis. In most cases the pain subsides spontaneously within a few days of conservative treatment consisting of rest and immobilization. Symptomatic therapy is given for the relief of pain. In the more persistent cases a cervical brace, or even head traction, may be useful. When the pain is severe and persists, surgical decompression of the nerve root is the treatment of choice. J. A. M. A.

Treatment, Neurosurgery

PREFRONTAL LOBOTOMY IN THE MANAGEMENT OF INTRACTABLE PAIN. E. HAMILTON and J. HAYES, Arch. Surg. **58**:731 (June) 1949.

Bilateral prefrontal lobotomy was performed on 16 patients for the relief of intractable pain, with a mortality of 18 per cent. Ten patients suffered from inoperable carcinoma; 3 had painful phantom limbs, and the remainder, various conditions, such as causalgia, quadriplegic spasm and tabetic crises. In most cases, Lyerly's "open" technic was used. Satisfactory relief of pain was obtained in 12 patients; yet no information is given concerning the time of postoperative observation. The postoperative mental changes constitute a strong objection against the use of lobotomy for relief of pain; in the authors' material, however, most of the patients made a satisfactory social recovery without serious mental symptoms. There seems to be no definite correlation between the relief of pain and the degree of mental impairment following the operation. In order to reduce the risk of postoperative change in personality, the authors recommend a more anterior plane

of incision for lobotomy; furthermore, they suggest that only the lower halves of both frontal lobes and the medial upper quadrant of one of the frontal lobes need to be cut.

Patients addicted to drugs exhibited no psychologic symptoms of drug withdrawal after lobotomy, but they still showed physiologic signs of withdrawal.

LIST, Grand Rapids, Mich.

TREATMENT OF PNEUMOCOCCAL MENINGITIS. J. KERSHMAN and E. PETERSON, Canad. M. A. J. **59**:527 (Dec.) 1948.

Kershman and Peterson report 12 cases of pneumococic meningitis which was treated during the last eighteen months at two Montreal hospitals. The ages of the patients ranged from 2 months to 73 years. Sulfonamide drugs and penicillin were employed in all cases. In 9 cases sulfadiazine was given in a dose of 2 Gm. initially and 1 Gm. thereafter every four hours. In 4 instances soluble sulfadiazine or sulfathiazole was given intravenously or intramuscularly because the patients were not able to take oral therapy. The intramuscular dose of penicillin varied from 5,000 to 100,000 units every three hours, the average dose being 30,000 units. In 9 of the 12 cases penicillin was also given intrathecally, and in 1 instance intraventricularly. The 1 death that occurred in this series was that of a 73 year old man, who was improving clinically from his meningitis but died of bronchial obstruction caused by the aspiration of mucus and sanguinous discharge which accumulated immediately after a simple mastoidectomy and endonasal antrotomy. In 1 patient transverse myelitis developed after the intrathecal injection of penicillin. This patient also had intellectual deterioration, presumably the result of cerebral damage arising from his infection. The authors feel that a successful outcome in the treatment of this condition depends on the intrathecal, as well as intramuscular, use of penicillin, and especially on early and radical treatment of the underlying focus of infection. The latter is usually found in the sinuses and mastoids.

J. A. M. A.

EFFECT OF LEUKOTOMY ON PSYCHOTIC SYMPTOMS. W. MAYER-GROSS, Encéphale **38**:317, 1949.

According to Mayer-Gross, the effects of cerebral leukotomy are due to the appearance of the classic symptoms of a lesion of the frontal lobe. The problem of the operation is quantitative; that is, if a quantitatively adequate frontal lobe syndrome will counteract or counterbalance the psychotic symptoms, the latter will become inoperative or will disappear. The reconstruction of the personality by means of the operation is possible only if the prepsychotic personality and its affective and conative integrity have somehow been preserved behind the façade of the psychosis. This element is equivalent to the "tension" which Freeman and Watts have indicated as a necessary criterion for operation. The frontal lobe syndrome is marked by euphoria, bland optimism, absence of refined and delicate affective reactions and lack of tact. In the motor domain, hyperkinesis, motor instability and disturbances of attention are symptoms of the lesion of the frontal lobe. Finally, in the intellectual sphere, "concreteness," lack of synthesis and inability to evaluate the symptoms themselves are characteristic.

The author feels that this apparently rather simple theory is borne out by his study of four groups of patients undergoing frontal leukotomy. The results for two groups, with a total of 68 patients, were compared. One group had been able

to leave the hospital; the other had not. The operation had been done one year prior to the report. Six of the hospital patients were very much improved but had no homes to go to. Ten retained their improvement by working in the hospital in a protective environment. Twenty-eight showed only slight improvement, while the condition of 2 was unchanged and that of 4 became worse. There was a marked difference in the results of the operation in the two groups. The hospitalized patients showed absence of extroversion, cheerfulness, hyperactivity, sociability and friendliness, traits which were all pronounced in the patients who were able to leave the hospital. The hospitalized group was characterized by laziness, inertia, lack of initiative and apathy. Since the two groups were operated on by the same surgeon, using the same technic, the author indicates that the difference in results lies in the differences in the preoperative clinical history and clinical condition of the two groups. The discharged group were sick for a shorter time; it included fewer schizophrenic patients, few hebephrenic patients and more patients with obsessional states and affective psychoses. Their personalities were, on the whole, far more intact than those of the hospitalized group.

A third group, of 52 patients, were subjected to a modified frontal leukotomy in which only the orbital region was sectioned and isolated while the superior part of the frontal region was left intact. At first the results were encouraging, but further study and follow-up observation showed that of the 18 paranoid patients out of 41 with schizophrenia, only 4 continued to show satisfactory improvement. This is a proportion far below that obtained by the classic operation. Even the patients with obsessional states showed poorer results. Thus, on the whole, the results of the orbital type of leukotomy accord with the author's thesis that it is necessary to isolate a sufficient quantity of the frontal lobe before worth while results can be obtained. He states that leukotomy not only adds new frontal lobe symptoms but also suppresses many psychotic ones.

The fourth group, of 11 patients, consisted of 8 with periodic catatonia and 3 with rigorously regular fluctuations of a manic-depressive psychosis. The classic type of frontal leukotomy suppressed all periodic and psychotic symptoms in the 8 catatonic patients and produced a notable improvement in the 3 with a manic-depressive psychosis. These results support the concept of a functional relation between the prefrontal cortex and the hypothalamus. It is also possible that the abolition of periodicity is part of the frontal lobe syndrome.

ZINKIN, New York.

MYELOTOMY OF THE POSTERIOR COMMISSURE. A. JENTZER, Confinia neurol. **8**:1, 1947-1948.

Jentzer reports 3 cases of pain problems in which section of the posterior commissure of the spinal cord was carried out. In the first case, one of syringomyelia, the pain was relieved by the procedure. In the second case, of chordoma, pain was relieved for only three weeks by section of the posterior commissure. Autopsy revealed that the tumor had invaded the cord and that the section of the posterior commissure had been complete. In the third case, in which an inoperable carcinoma of the rectum was associated with severe pain, a posterior commissure section gave relief from the pain. The patient died four days later, and autopsy revealed degeneration in the posterior columns. On the basis of these cases, the author questions the validity of present concepts of the sensory pathways in the spinal cord.

FOLEY, Boston.

BILATERAL FRONTAL LOBOTOMY IN CASES OF CANCER OF THE LUNG. J. A. TAIANA, R. C. BORAGINA and E. SCHIEPPATI, Prensa med. argent. **35**:449 (March 12) 1948.

Bilateral frontal lobotomies were performed on 3 men, aged 43, 47 and 52, respectively, because of severe thoracic pain accompanying carcinoma of the lung. The duration of illness varied from two months to two years. One patient died on the third postoperative day; before his death he was conscious of thoracic pain but did not suffer as intensely as before the operation. Twenty-four hours after the operation, 1 of the other patients had no pain, and the third complained of pain but stated that it was minimal. One of the patients could not move the upper limb on the affected side because of pain; after the operation the limb could be moved freely. The longest postoperative period prior to preparation of the report was forty-two days. The authors believe that lobotomies will be perfected so that it may be possible to interrupt only pathways which conduct pain and abnormal sensations from the internal organs.

N. SAVITSKY, New York.

EFFECT OF BLOODLETTING ON LATE RESULTS IN CRANIAL TRAUMA. D. M. GROZDOV, Khirurgiya, 1947, no. 1, p. 46.

Grozdov reports on 234 patients with cranial trauma treated by bloodletting. Removal of as much as 400 cc. of blood had little influence on the arterial pressure. The often dramatic improvement in the condition of a patient with cerebral concussion and increased intracranial pressure suggested that the effect was due to lowering of the venous rather than the arterial pressure. Bloodletting appears to relieve the venous stasis resulting from edema of the brain and compression of the sinuses. Actual determinations of the venous pressure demonstrated a decided lowering as a result of bloodletting. The author concludes that determination of the venous blood pressure furnishes more information about the state of intracranial pressure than determination of the arterial pressure. A common sequela of cranial trauma, as observed in 82 patients followed for from two to four years, was that of dizziness and headache. A follow-up study of the author's material showed that these complications were seen much less frequently than in patients not treated by bloodletting.

J. A. M. A.

HISTAMINE AND ANTIHISTAMINE TREATMENT OF HEADACHE. OLE ESMARCH, Acta psychiat. et neurol. **23**:235, 1948.

In 12 patients with headache who had had no relief from other methods of treatment, histamine produced relief of the headache. After two months, it was found that 6 patients still had relief from the headache, 5 had had recurrence after one month and 1 had a recurrence within a few days.

ALPERS, Philadelphia.

Encephalography, Ventriculography, Roentgenography

DIAGNOSIS OF SUPRA-SELLAR TUMORS BY PNEUMOENCEPHALOGRAPHY. N. S. SCHLEZINGER and J. G. TEPLICK, Am. J. Roentgenol. **60**:213 (Aug.) 1948.

Schlezinger and Teplick describe 5 suprasellar tumors, 4 of which were verified suprasellar meningiomas and the other an unverified tumor of the hypophysial duct. In all cases the cisterna chiasmatis appeared obliterated in routine pneumoencephalograms. In a control series of 150 consecutive encephalograms, the cisterna chiasmatis was visualized in 94 per cent.

Non-neoplastic conditions, particularly optochiasmatic arachnoiditis, may obliterate the cisterna chiasmatis. The authors conclude that this finding warrants the presumptive diagnosis of suprasellar tumor if a lesion in this area is suspected on clinical grounds. Conversely, clear visualization of the cistern practically excludes the diagnostic possibility of a suprasellar lesion in this vicinity.

TEPLICK, Philadelphia.

LUMBAR INTERVERTEBRAL DISC PROTRUSIONS CONTRALATERAL TO THE SIDE OF SYMPTOMS AND SIGNS. J. P. MURPHY, Am. J. Roentgenol. **61**:77, (Jan.) 1949.

Murphy emphasizes the importance of myelographic verification of lesions of the disk. In 2 patients there were classic signs and symptoms of a left-sided lesion of a disk in the lumbar area on the left side. Myelograms showed definite defects in the column of oil on the opposite side, confirmed by surgical exploration.

TEPLICK, Philadelphia.

PARAPLEGIC NEUROARTHROPATHY. J. SOLOVAY and H. U. SOLOVAY, Am. J. Roentgenol. **61**:475 (April) 1949.

The neuropathic articular and periarticular changes in paraplegia have been variously described as "paraosteoarthropathy," "neurogenic myositis ossificans" and "para-articular calcification."

In 9 patients with complete paralysis and anesthesia of both lower extremities the hip joint regions only were affected. The changes consisted of small bony plaques adjacent to or contiguous with the greater trochanter, often bilateral and symmetric. In several patients the bony outgrowths extended toward the pelvis or into the muscles of the thigh. Only 1 patient showed erosion of the articular surfaces characteristic of an atrophic Charcot joint (neurogenic arthropathy). All the patients showed some degree of osteoporosis. Of the 9 patients, 7 showed periarticular calcification.

The authors believe that these neuropathic and periarticular changes in the lower extremities of paraplegic patients constitute another manifestation of the Charcot neuroarthropathy. In the paraplegic, periarticular ossification is the outstanding feature, and intra-articular destructive changes are minimal or absent, though occasionally striking.

Paraplegic neuropathy is believed due to long-continued pressure over anesthetic bony prominences with absence of warning sensation. This is equivalent to trauma in initiating ossification in the periarticular tissues. The scarcity of intra-articular changes is attributed to lack of use of paralyzed joints.

TEPLICK, Philadelphia.

MOBILE CALCIFIED CHOROID PLEXUSES. M. MABLIN, Radiology **51**:383 (Sept.) 1948.

Mablin noted marked depression of one choroid plexus and at a later date of the other. Studies carried out with the skull in various positions, and with air in the ventricular system, disclosed that calcified choroid plexuses moved considerably simply through gravity. The maximum motion of each calcified plexus was 3.0 cm. in the vertical plane, 2.4 cm. in the anteroposterior plane and 2.0 cm. in the transverse plane. There was no space-taking intracranial lesion. Apparently, in this case, the calcified glomi of the choroid plexuses of the lateral ventricles were pedunculated, permitting extensive movement with gravity.

TEPLICK, Philadelphia.

ROENTGENOLOGIC DIAGNOSIS OF PITUITARY TUMORS. H. F. HARC, E. SILVERS and M. I. SMEDAL, Radiology **52**:193 (Feb.) 1949.

The authors studied the dimensions of the sella turcica from lateral and posteroanterior stereoscopic roentgenograms, made with the central beam passing through the sella. The lateral outline of the sella was transferred to millimeter paper and the area measured in square millimeters. The average normal was 74 sq. mm. An area of 130 sq. mm. or more was arbitrarily chosen to indicate an enlarged sella.

In the modified posteroanterior projection the floor is distinctly seen, and any irregularities of its contour are easily detected. From this projection, the authors made the following measurements on adults: (*a*) distance between the anterior clinoid processes, the average being 2.6 cm. and the upper limit 2.8 cm.; (*b*) width of the posterior clinoid processes, the average being 18 mm., and the range from 15 to 20 mm.; (*c*) width of the dorsum just below the posterior clinoid processes, the average being 15 mm. and the range from 9 to 18 mm.

In 32 cases of pituitary tumors, some or all of these measurements from the posteroanterior or the lateral projection were above normal. In many there were the classic signs of erosion of the clinoid processes and dorsum, in addition to enlargement of the sella. Of 33 other cases in which the lateral area of the sella was above 130 sq. mm., only 5 had clinical symptoms suggesting tumor or disease of the pituitary gland. The authors were uncertain about the significance of the large number of apparently normal persons with an enlarged sella turcica. These persons may be harboring an asymptomatic adenoma and should be followed carefully.

TEPLICK, Philadelphia.

SUBDURAL AIR SHADOWS AND CORTICAL ATROPHY. PAUL MARTIN and WILLY GEETS, Acta neurol. et de psychiat. Belg. **48**:493 (Oct.) 1948.

The presence of subdural air shadows after the lumbar injection of air has been described previously, but their significance, their therapeutic interest and the method of penetration of the air into the subdural cavity are problems which are poorly understood. Three possibilities exist in regard to the mode of introduction of air into the subdural space: (1) permeability of the cranial arachnoid tissue; (2) a tear of the arachnoid, permitting the escape of the gas, and (3) injection of air into the lumbar subdural space. Subdural air is characterized by distinct borders and motility with change of position of the head. It is found in subjects with various neurologic diseases, and its presence does not indicate the existence of cerebral atrophy. A subdural air shadow with normal characteristics and motility is not of diagnostic significance and may indicate only a particular fragility of the arachnoid.

DEJONG, Ann Arbor, Mich.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Paul C. Bucy, M.D., *President, in the Chair*
Regular Meeting, Dec. 9, 1947

Abscess of the Midbrain: Report of a Case. Dr. Meyer Brown.

A case is presented of a solitary pyogenic abscess which occupied almost the entire midbrain in a 21 month old male infant. The case is of interest because of the unusual location of the abscess, because it occurred with no demonstrable point of origin and because it was the terminal illness in a patient with congenital heart disease but no evidence of endocarditis. Arteriovenous shunting, producing cyanosis on exertion only, occurred through a patent interventricular septum, which was associated with a transposed aorta and absence of one pulmonic valve cusp. The total duration of symptoms due to the abscess in the midbrain was twenty-one days.

DISCUSSION

Dr. Victor E. Gonda: Were the micro-organisms identified?

Dr. Meyer Brown: I did not identify any of the organisms in the blood cultures, and no cultures were made from the abscess post mortem. In a suitably stained microscopic slide, no organisms were seen. It is surprising that one does not see more abscesses of the brain in patients who die of the complications of congenital heart disease. A vegetative endocarditis is far more frequent in these patients than is a cerebral abscess.

Reconstruction of the Diencephalic Nuclei of the Macaque. Dr. Wendell J. S. Krieg.

As a background for reconstructions of the connections of the cerebral cortex in Marchi series, the diencephalon of the macaque was graphically reconstructed in frontal slices.

Of the median group, the nucleus paraventricularis is divided into the stellatocellular and the rotundocellular portion, the latter of which includes the nucleus intermedialis and the nucleus paramedianus. The nucleus rhomboidalis, the nucleus centralis medialis and the nucleus submedius are small. The nucleus centralis lateralis does not extend between the medial and the lateral nucleus. The nucleus medialis is large and extends caudolaterally. The nucleus ventralis contains the pars anterior, the pars ventralis, and the pars dorsomedialis; the three divisions of the nucleus lateralis posterior, the arcuate, the lateral and the inferior, and the newly recognized glomus fili.

The nucleus lateralis contains the pars dorsalis, the pars anterior, the pars medialis, the pars lateralis and the pars dorsalis. The last of these is subdivided into three laminas. Small and large cell divisions of both the median and the lateral geniculate bodies are recognized. There is a nucleus suprageniculatus and possibly a nucleus limitans, but no nucleus posterior thalami.

The hypothalamus is composed of five sagittal laminas, with characteristic cell types, but individual nuclei are differentiated from the matrix of each lamina.

The hypothalamic nuclei are conservative and hence differ little from those in other forms, and they are well characterized in sections.

A comparison with rat and man shows that the monkey occupies an intermediate position with respect to the degree of development of the individual nuclei of the diencephalon.

DISCUSSION

In reply to questions from the floor, Dr. Krieg replied briefly, comparing the extent of development of the large and small cell portions of the geniculate bodies with the development of discriminative and protopathic sight and vision.

Intracranial Complications in Osteoma of the Paranasal Sinuses. DR. IRVING SPIESMAN and DR. HANS BRUNNER (by invitation).

Paul C. Bucy, M.D., *President in the Chair*

Regular Meeting, Jan. 13, 1948

Diffuse Demyelinating Disease of the Central Nervous System (Pelizaeus-Merzbacher Type?): Report of a Case. DR. IRVING C. SHERMAN and DR. ERIC LIEBERT.

A white girl had been in normal health up to the age of 7 years, when she manifested evidence of disease of the nervous system. First, there appeared severe cerebellar ataxia in all four extremities, together with signs of involvement of the pyramidal tract and mild evidences of dementia. Within a few months she became bedridden with severe spastic paraplegia in extension, with the feet in equinovarus. The upper extremities were in either severe flexion or extension. There later appeared spontaneous circular movements of the extended arm on each side, accompanied with a torsion movement of the pelvis. She became incontinent and lost her speech. Except for a fine nystagmus, there were no signs of disease of the cranial nerves. She died fifteen months after onset. A brother had died five years previously, at the age of 7, with a similar clinical picture. Seven other siblings were well, and there was no other familial illness.

Pathologically, there was severe demyelination throughout the corpus striatum, internal capsule, centrum semiovale and corpus callosum. In the internal capsule there were intact islands of myelinated fibers. The cerebellum was demyelinated, as were the pyramidal tracts in the brain stem and the spinal cord except for the posterior columns. Nissl stains revealed a fairly normal cortex. The cells of the dentate nucleus showed swelling of the cell body, which apparently contained a large amount of lipid substances with displacement of the nucleus. The Purkinje cells showed chromatolysis. Perivascular infiltration was present, chiefly in the white matter. Gitter cells occurred in some parts of the white matter, whereas in others the process seemed to have ended and a slight increase in astroglia cells could be noted.

The diagnosis was familial subacute diffuse primary demyelinating disease. The classification of the diffuse demyelinating diseases was discussed. The futility of attempting to categorize them by incidental pathologic findings was pointed out.

DISCUSSION

DR. RICHARD B. RICHTER: It is not clear to me why Dr. Sherman classifies this case of nonfamilial diffuse demyelinating disease as of the Pelizaeus-Merzbacher type. It would seem more natural to regard it as belonging to Schilder's disease (progressive subcortical encephalopathy), if, indeed, there is a difference. A good deal of attention has been paid to the swelling of cells of the dentate

nuclei. Is this not merely the nondescript swelling observed almost routinely in the brains of patients who die of any acute illness, especially if associated with fever?

DR. WALTER R. KIRSCHBAUM: This case should be classified as leukodystrophia progressiva, likely to be hereditary or familial. According to Bielschowsky, a primary nutritive disturbance of the glia of the white substance should be considered. It is of special interest to learn about changes of the oligodendroglia and microglia with respect to demyelination and their activities in such disturbances of metabolism.

DR. IRVING C. SHERMAN: Some one asked whether the patient was deaf; she was not. Dr. Richter asked why we classified the case as we did, rather than as one of Schilder's disease. I can only refer to my opening statements. I attempted to show that the classification is really invalid, because clinically and pathologically all these demyelinating diseases are one. We believed that the process was in the category of the Pelizaeus-Merzbacher type of demyelination because clinically it was familial and Schilder's disease is not, and pathologically there was preservation of islands of myelin. Perhaps the only significant differentiating factor was the familial character.

DR. ERICH LIEBERT: Dr. Kirschbaum commented on the ballooning of the ganglion cells, which is similar to change seen in amaurotic familial idiocy. A large amount of fat was present in these ballooned parts. We classified the condition as progressive cerebral leukodystrophy (Pelizaeus-Merzbacher disease) because in some parts of the degenerated substance islands of myelin sheaths were still present, though not so conspicuously as in other cases described. Because of the ballooning of the ganglion cells and the presence of the lipids, which were also to be seen in the perivascular spaces, it must be considered that a possible connection exists between this form of diffuse schlerosis and amaurotic familial idiocy.

Point of Action of 3-O-Toloxy-1, 2-Propanediol (Lissephen®) Effects on the Nervous System. DR. ISIDORE FINKELMAN and DR. ALEX J. ARIEFF.

This paper was published in full in the June 1949 issue of the ARCHIVES, page 680.

DISCUSSION

DR. R. K. RICHARDS: I should like to mention the results of experiments conducted in the pharmacologic department of Abbott Laboratories by Dr. Everett and myself. Lissephen® is identical with the British "myanesin." As the authors reported, we also were able temporarily to abolish rigidity after decerebration by means of injection of lissephen®. The toxicity of the drug depends greatly on the rate of injection. Rapid injection of a dose that is easily tolerated if given more slowly will kill the animal. After rapid injection an acute circulatory collapse occurs, as well as rigidity, which may be due to temporary cerebral anoxia. We have also found it easier to antagonize the effect of lissephen® with strychnine than with metrazol®. If one stimulates the posterior root after laminectomy in cats and dogs, one notices an increase in the threshold after injection of lissephen®. Electroencephalographic records show that with injection or infusion of high doses of the drug slow large waves appear, as in drowsiness and sleep. Thus we believe that the action is both on the spinal cord and, to a certain degree, more centrally, on the brain.

Except in extremely high doses, there is no peripheral curare-like effect with this drug. Its action is very short, and large doses must be used to produce any effect after oral administration. It appears that the majority of anesthetists who

have used lissephen® or "myanesin" instead of curare are not particularly impressed with its action. The possibility of cardiac and circulatory depression after the administration of large doses must be considered. However, it may be possible that lissephen® would be useful in certain conditions, such as spastic diseases. This point deserves further study.

DR. A. E. BENNETT: The action of this drug is not that of curare. I do not believe it is even curare-like. One does not see any central effect with curare, such as that on respiration. Its action is purely on the motor end plates and muscle. I do not believe that curare is a lethal drug. I have kept animals alive for thirteen hours with artificial respiration. One can kill animals, as Dr. Finkelman has done with lissephen®, by rapid injection, producing circulatory collapse. I believe that the action of lissephen® is on the spinal cord.

DR. L. J. POLLOCK: I might say that we have no interest in the clinical application of this drug. Despite the fact that there is a wide range between the dose of curare which is dangerous and that which is used clinically, no one has reported on the effect of curare on the regeneration of motor end plates in denervated muscles.

DR. ALEX J. ARIEFF: Lissephen® has a central action, chiefly on the spinal cord, whereas curare acts on the myoneural junctions of cranial and peripheral nerves. Curare produces cranial nerve paralyses, especially of the extraocular muscles, and even pharyngeal paralysis. This always makes one apprehensive. I have not had as much experience as Dr. Bennett, but because of the absence of cranial nerve paralyses with the use of lissephen,® we feel that this drug merits further clinical investigation.

Proneness to Accident in Multiple Sclerosis: Relation to Trauma, with Medicolegal Implications. DR. A. E. BENNETT.

The remitting progress, unknown cause, personality changes and spastic ataxic symptoms predispose persons with multiple sclerosis to accidental injury, thereby tending to confuse the causal relation of accident and the disease. In more than 10 per cent of cases trauma is claimed to cause the onset of symptoms. Despite lack of scientific evidence that trauma causes or aggravates the disease, the courts often award full compensation in these cases.

From wide medicolegal experience, the author described 3 cases. In 2 cases the courts sustained evidence that the accidents occurred because of the disease and did not aggravate the condition. Trauma was accepted in 1 case as the cause of total, permanent disability. Of 17 additional cases collected from court records and state labor commissions, the settlement was for the claimant in 11 and against the claimant in 6.

An extensive review of the literature shows great variation in the etiologic role assigned to trauma in multiple sclerosis.

A characteristic overconfidence and impaired judgment, together with motor paresis, ataxia and disturbed equilibrium, combine to make the patient prone to accidents, especially those of slipping and falling. The tendency is to ascribe the symptoms to the accident and not the reverse. Courts are thus misled into erroneous decisions.

There is need for unified medical opinion to guide judicial settlements. A committee set up prior to the war should resume investigation of the relation of trauma to various organic neurologic diseases and thereby develop a unified

medical opinion. Expert witnesses should be drawn from a panel of qualified neurologists certified by a medical society. Their impartial, unified opinion should replace the present method of retaining expert witnesses on a partisan basis.

DISCUSSION

DR. R. P. MACKAY: Dr. Bennett's cogent conclusions undoubtedly meet with general agreement. It is often difficult, however, for the physician to testify in a medicolegal case in which trauma is alleged to have caused or exaggerated multiple sclerosis. Attorneys have a way of phrasing their questions in an effort to induce the physician to swear that it might be possible for trauma to have initiated or influenced the disease. Since no one knows the cause of multiple sclerosis, one can scarcely answer such a question. However, since there is no evidence in favor of such a causal relation, I believe that answers should be in the negative. Physicians, when they testify, must avoid such pitfalls and attempts to phrase their answers so as not to bring about injustice.

DR. HERMAN JOSEPHY: It seems to me that the legal situation with regard to disseminated sclerosis is similar to that which existed many years ago with Huntington's chorea. There was much discussion as to whether chorea could be caused by trauma, and it was some time before it was generally accepted that a choreic patient did not fall sick because he suffered an accident, but had an accident because he already was choreic. As a matter of fact, the accident rate among patients with early chorea is high, and the time interval between trauma and manifest disease is apparently, but not actually, short enough to suggest to the layman a causal connection.

I should like to ask Dr. Bennett whether he thinks that a patient with disseminated sclerosis may become worse by exposure to cold or rain or after overexercise.

DR. VICTOR E. GONDA: How can medical men, or medical societies, prevent any one from asking hypothetic questions, especially in cases of disease of unknown origin?

DR. A. E. BENNETT: I do not know what we physicians can say about exacerbation of symptoms, whether by cold or by excitement. Such relapses have always seemed to me to be coincidental. I think that the physician attempts too much to say what is the cause.

With respect to hypothetic questions, I agree we cannot get rid of them, but I think we can modify the technic and refuse to answer if facts are not truly presented, so that we will not be pinned down. If we can bring enough medical opinion to bear, we can modify the procedure and avoid bias.

Paul C. Bucy, M.D., President in the Chair
Regular Meeting, Feb. 10, 1948

Compression or Degeneration of the Spinal Cord. DR. PAUL C. BUCY.

Four cases of compression of the spinal cord by median herniations of cervical intervertebral disks were presented. The symptomatology of such lesions was summarized. Median herniation of a cervical intervertebral disk is characterized predominantly by spasticity and hyperreflexia in the lower extremities and by unsteadiness of gait. Sensory changes are commonly mild or absent. Pain, tenderness and stiffness of the neck, which are common with laterally lying

herniations, are very uncommon with median herniations. Paresthesias, muscular weakness and awkwardness in the upper extremities may occur, but involvement there is much less marked than in the legs. Evidence of obstruction of the spinal canal on Queckenstedt's test is not present in many cases, but lipiodol® (iodized oil U. S. P.) or pantopaque® (ethyl iodophenylundecylate) will reveal an obstruction or deformity of the spinal canal in a majority of cases, but not in all. The spinal fluid is normal except for moderate elevation of the protein content in some cases. These herniations are best removed transdurally through a bilateral laminectomy of at least two vertebrae. The results of such an operation in early cases should be excellent, but in cases of severe compression of long standing poor results have commonly been reported.

The differentiation of median herniation of the cervical intervertebral disks from degenerative diseases of the spinal cord, such as multiple sclerosis, primary lateral sclerosis and amyotrophic lateral sclerosis, is not easy. This problem was discussed. In every case in which there is any reason to suspect that a median herniation of a cervical intervertebral disk might be at fault, a fluoroscopic examination of the spinal canal with pantopaque® should be made.

DISCUSSION

DR. VICTOR E. GONDA: Some time ago, in the diagnosis of herniated cervical disk, Dr. Bucy stated that the presence of pain localized near the scapula was of great importance. This he did not mention tonight, and I should like to ask the reason for the omission.

In the last 3 cases was the disk removed entirely, or only in part?

Is there any possible explanation for the presence of the sensory loss at a lower level than that to be expected from present anatomicophysiologic knowledge?

I should be very doubtful about a favorable prognosis in a case in which the deltoid muscle is atrophied; this muscle is notoriously slow in regeneration.

Since the spinal cord was not directly involved in the cases reported, the fibrillation must have been caused by irritation of the roots. This is a fact which I think should be emphasized.

DR. RICHARD B. RICHTER: Dr. Bucy remarked that midline protrusions of cervical disks may occur at a level as high as the interspace between the fourth and the fifth vertebral body. Have they been found even higher, or would a sensory level as high as the second or third dermatome be good evidence that the lesion was not of this type?

DR. PAUL C. BUCY: Pain along the medial border of the scapula, which is commonly associated with laterally placed herniations of cervical intervertebral disks which compress one of the lower cervical roots, has not been seen in any of my cases in which the herniated disk was in the medial portion of the spinal canal. In all cases of medially lying herniations of the cervical intervertebral disks the herniated mass of cartilage has consisted of a number of cartilaginous chips molded together into a single mass. These chips have been removed piecemeal. In none of my cases was the herniation a single piece of cartilage.

I am at a loss to explain the development of the sensory level far below where one would expect to find it in view of the location of the compression of the spinal cord. Others observers have noted a similar condition in cases of this kind. Certainly, the observation of muscular fibrillation as the result of compression of one or more anterior cervical roots is evidence that such fibrillation can appear with conditions other than degeneration of the anterior horn cells.

In the present cases the highest level at which I have found a herniated intervertebral disk was between the fourth and the fifth cervical vertebra. However, cases have been reported with herniations between the third and fourth cervical vertebrae, and I do not see why in an occasional case there might not be a herniation between the second and third cervical vertebrae. There could be no such herniation between the first and second cervical vertebrae, as there is no disk at this point.

Crossed Gluteal Reflexes. DR. HAROLD J. LAWN.

The gluteal reflex, as ordinarily described, is homolateral, and the reflexogenous zone is the buttock. It is considered analogous to the cutaneous abdominal reflex. During examination of the reflex activities of veterans who had sustained an injury to the spinal cord, a crossed gluteal reflex was elicited in 2 cases by cutaneous stimulation of the lower extremities and buttocks.

In the first case, application of deep pressure, pinprick and evaporating ether to the sole, the internal and external malleolus, the inner and outer aspects of the leg, the inner surface of the thigh and the inferior border of the gluteal fold on the right side produced a sharp contraction of the gluteus maximus and gluteus medius on the left side and, occasionally, of the lateral head of the hamstring muscles on the same side. The stimulus of election was evaporating ether, and the next in strength was pinprick. Occasionally, application of evaporating ether at the inferior border of the right gluteal fold caused such intense contraction of the left gluteus that the muscle would not relax for one or two minutes.

In the second case, evaporating ether, pinprick and deep pressure applied over the reflexogenous zones of the sole, the inner aspects of the leg and thigh and the lower border of the gluteal fold on one side caused crossed responses of the gluteus maximus and medius. The strongest responses were obtained from evaporating ether applied at the lower border of the gluteal fold.

Because of the unusual character of these responses, careful studies were made in 11 cases with extensor reflex patterns, both crossed and homolateral, to determine the degree to which the contraction of the gluteal muscle participated. In 1 case a palpable increase of tone occurred in the contralateral gluteal muscle; in another, along with contraction of the anterior muscles of the thigh and calf, there was a visible contraction of the gluteal muscle, both contralateral and ipsilateral. In none of the cases was there an isolated response of the gluteal muscles, such as has been described. Furthermore, this reflex was not noted by other examiners in 300 cases of injury to the cord and cauda equina.

This reflex is a predominant and almost isolated contraction of the gluteal muscles. It is not part of a crossed extensor reflex, because it was not observed in cases which the latter occurred and, likewise, because in the 2 cases described the muscles usually contracting in a crossed extensor reflex did not participate. The reflex was elicited from an extensive reflexogenous zone, and the local signature of the reflex was lost.

In the first case, in which there was imperfect recovery of sensation, one may compare the gluteal reflex to certain homolateral reflexes, as described by Buzzard. Pollock described cases in which contralateral reflexes of the upper extremity were elicited by stimulation of the receptive zones below the level of the lesion. Whereas the radiation of nerve impulses was upward in previous cases, in these cases radiation was downward or at the level of the muscles involved. However, since in the second case there was no recovery of sensation, this explanation is inadequate. Since the pathways are as yet unknown, this observation records an unusual and interesting crossed reflex.

DISCUSSION

DR. PAUL C. BUCY: In watching the excellent motion pictures of this reflex, I thought that the muscular response gradually increased in intensity after application of the stimulus, finally reached a summit, which persisted for a time after the stimulus was removed, and then slowly relaxed. Although this type of response might be explained by the persistence of the stimulus in the case of ether, which remains in contact with the skin, such an explanation does not seem applicable when the stimulus is pinprick. If the author has been able to confirm this, has he any explanation for it? Although such prolonged muscular contraction is commonly seen in the flexor group of muscles after termination of the stimulus, it is not common in the extensor group, of which the gluteus muscles are a part.

DR. VICTOR E. GONDA: There is a movement which already has many followers among the neurologists who claim that all reflexes are muscle stretch reflexes. How could one classify as such a reflex this interesting phenomenon, in which a small amount of ether is applied to the skin and contraction of the gluteal muscles ensues?

DR. HAROLD J. LAWN: Sherrington, Denny-Brown and Liddell have done extensive work on spinal reflexes and the involvement of the extensor muscles; Walshe has also contributed. It was their expressed opinion that there is gradual recruitment of neurons. Apparently, large numbers of neurons come into the picture and continue to discharge impulses even after the stimulation is discontinued.

Dynamic Pathologic Changes in the Brain in Chronic Brucellosis. DRS. NATHANIEL S. APTER, C. WESLEY EISELE, NORMAN B. MCCULLOUGH and WARD C. HALSTEAD.

Since Hughes isolated the Brucella organism from the human meninges in 1897, a number of neurologic syndromes have been described in association with chronic brucellosis. The literature on the neuropathologic changes in chronic brucellosis was summarized.

Correlative studies utilizing medical, neuropsychiatric and experimental psychologic technics indicate that the cerebral involvement associated with chronic brucellosis is chronic and progressive. The combined technics provide a method for distinguishing between changes in behavioral patterns due to cerebral damage and the psychoneurotic reactions which follow. Illustrative case material was presented to support a dynamic view of the cerebral pathology in chronic brucellosis.

DISCUSSION

DR. WARD C. HALSTEAD: I might point out that the general clinical status of the patients described by Dr. Apter was such that we could get excellent test cooperation throughout. Furthermore, our test battery is so designed as to provide much control information on a considerable variety of tests in addition to those which enter into the impairment index score. For these, and other, reasons stated by Dr. Apter, we feel confident in setting our findings before you.

DR. PAUL C. BUCY: Is the defect or deficit greater with increase in the index or with the smaller figures toward the left?

DR. WARD C. HALSTEAD: As our impairment index increases, the behavioral defects or deficits also are increased. Greater behavioral deficits were observed in the patients as the impairment index increased from left to right.

DR. N. B. MCCULLOUGH: We have treated some of these patients, but since the post-treatment observation period is not very long, it is not known whether the change is reversible or irreversible. We hope to be able to answer that at a future date.

DR. NATHANIEL S. APTER: A question was asked about fever therapy. We have not used this in treatment. Drs. Eisele and McCullough have tried combinations of the antibiotic agents. In conjunction with medical treatment, we have instituted a psychotherapeutic program for these patients in order to facilitate adjustment to their recently acquired cerebral damage.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Charles L. Kubik, M.D., *Presiding*
Regular Meeting, Dec. 18, 1947

Clinical and Pathologic Aspects of Influenzal Meningitis. DR. RAYMOND D. ADAMS, DR. CHARLES L. KUBIK, and DR. FRANCES J. BONNER.

This paper was published in full in the *Archives of Pediatrics* (**65**:354 [July] 1948).

Biochemical Changes in Electric Shock Therapy. DR. RUDOLPH NEUSTADT, DR. ABRAHAM MYERSON, MISS L. GLADYS HOWARD, DR. RUDOLPH KALDECK and DR. LEO ALEXANDER.

The physiologic links between application of the electric current and clinical recovery have been little explored. We studied several groups of biochemical substances during and after electric shock therapy. Each group, however, was studied only until a definite trend, or its absence, became evident, and then we proceeded to the study of another substance. Those substances which showed a definite trend will be studied more closely. Whenever possible, blood was drawn simultaneously from the brachial artery, an antecubital vein and the internal jugular vein by the technic introduced by Myerson. Most changes during electric shock therapy are brisk but short-lasting; therefore, exact timing with a stopwatch is necessary. Only with exact timing can reproducible results be obtained, and only under standardized conditions can the results of one set of investigators be compared with those of another.

While the oxygen content of the arterial blood dropped slightly during the tonic phase and more decidedly during the clonic phase, the oxygen content of the internal jugular venous blood dropped precipitously during the tonic phase and rose strikingly during the clonic phase and in the postconvulsion period. Thus, during the tonic phase there was a great increase in arteriovenous difference, followed by a great diminution in this value, during the clonic phase and the postconvulsion period. All values returned to their basic levels within five minutes after the convulsion.

The carbon dioxide content dropped and remained low for about thirty minutes after treatment, while the blood sugar rose continuously for at least half an hour. This long-lasting hyperglycemia may have therapeutic significance.

Creatinine did not change in the arterial or peripheral venous blood during and after electric shock therapy in 80 per cent of all subjects. However, in 90 per cent of all subjects a surprising increase of creatinine was found in the inter-

nal jugular venous blood. This rise was 20 to 30 per cent of the initial value, was present at the end of the convulsion and lasted not longer than one minute. This phenomenon indicates cellular damage and a local breakdown of nuclear substances through electric shock.

Changes in hemoglobin occurred in the peripheral blood exclusively; they were not accompanied with a change either in the hematocrit reading or in the erythrocyte count; they varied greatly with the seasons and seemed to have no significant relation to the therapeutic effects. The total white cell count showed an increase, and the differential white cell count, a reversal of the figures for polymorphonuclear leukocytes and lymphocytes, lasting as long as eight to ten minutes.

The total protein content underwent significant changes—at first a rise, then a drop and then a sharp rise. These variations were almost exclusively caused by variations in the globulin, especially of the internal jugular venous blood. Here, after three minutes, a critical low level of globulin sometimes occurred, a fact which may account for the otherwise unexplained sudden deaths after electric shock therapy.

Cholinesterase dropped about 50 per cent during the first three minutes and remained low for forty-five to ninety minutes. The output of 17-ketosteroids in the urine dropped considerably after five or six treatments and remained low for six to eight weeks after the termination of therapy. This decrease probably indicated damage to the adrenal glands.

The increase in glucose and the decrease in cholinesterase were so perfectly reciprocal chronologically and quantitatively that this reciprocity must be of biologic significance in the chain of events. Likewise, the alterations in creatinine in the internal jugular venous blood and the changes in globulin, in the albumin-globulin ratio and in the white blood cell count probably form another unit of biologic significance, of change in cellular permeability, of destruction of intracellular substances and of compensatory restitution.

Madelaine R. Brown, M.D., *Presiding*

Regular Meeting, Feb. 19, 1948

Demyelination by Means of Enzymes. Dr. L. Raymond Morrison and Dr. Paul C. Zamecnik.

Following the technic of Weil, blocks of fresh, unfixed rabbit spinal cord were incubated with various enzymes under optimal conditions for twenty-four hours. The enzymes used chiefly were cobra venom and alpha toxin of Clostridium welchii. Similar blocks of cord tissue were also incubated in appropriate control mediums. In addition to the block method, sections of unfixed rabbit spinal cord were cut in the cold box, according to the technic of Linderstrom and Lang, and incubated in cobra venom or alpha toxin of Cl. welchii for shorter periods. Appropriate controls were run with these sections.

After incubation with the enzyme, the tissue was fixed in dilute solution of formaldehyde U. S. P. With the block technic, frozen sections were cut, and the rest of the block was embedded in paraffin or pyroxylin. With the cold box technic, sections were stained directly after fixation. The stains used were chiefly sudan II for fat and the Spielmeyer or Weil stain for myelin sheaths.

One of the active principles of cobra venom is the enzyme lecithinase, which is specific for its attack on the beta (unsaturated) fatty acid of lecithin. After hydrolysis the lecithin is broken down to lysolecithin, the fatty acid having been

split off. The active principle of the alpha toxin of Cl. welchii is also a lecithinase, but this enzyme attacks specifically the phosphorylcholine radical of lecithin, leaving behind the fatty acids and glycerol.

With the Weigert stain for myelin sheath, loss of myelin was seen around the periphery of the sections taken from the block of both cobra venom and alpha toxin preparations, the deeper parts of the section, which had not been exposed to the enzyme, retaining the color for normal myelin. The sections cut in the cold chamber showed widespread spotty demyelination, while control sections were free from myelin defect.

With the sudan stain there was brilliant red staining for fat in the exposed parts of the cobra venom preparations, but the Cl. welchii toxin preparations presented no fat at all. In other words, the products split off by the cobra venom enzyme (for fatty acids) were made visible with the sudan stain, but the phosphorylcholine radical split off by the alpha toxin of Cl. welchii, since it did not take the sudan stain, remained invisible. In order to visualize the phosphorylcholine, Gömöri's technic for phosphatase was used in reverse. In Gömöri's original method, the substrate is added to the enzyme, which is in situ in the tissue. With the reverse technic, used in the present study, the enzyme (lecithinase) is added to the substrate (lecithin), which is in situ in the myelin sheath. This results eventually in a black precipitate, cobalt choline sulfide, which is clearly visible in the parts of the tissue originally exposed to the action of the alpha toxin.

Thus it is seen that demyelination, as detected by myelin pallor in the Weil or the Spielmeyer stain, is common to both types of lecithinase reaction. The split products in neither reaction, however, are not visualized by a common stain. In 1 case sudan II was used to detect the fatty acid that was split off, while in the other case the sudan reaction was negative and a reverse Gömöri technic for phosphatase was used to make visible the phosphorylcholine that was split off. It is obvious, therefore, that the term "demyelination" does not always mean precisely the same thing. Since in the present work two types of demyelination were brought about by the action of two different enzymes, it is likely that other types of myelin breakdown can be produced by still different enzymes.

DISCUSSION

DR. J. FOLCH: Dr. Morrison summarized in fifteen minutes what has been a long task with great technical difficulties. Would Dr. Morrison think it worth while to try to use enzymes that are closer to those present in brain tissue? Snake venom is not present in mammalian tissue. The alpha toxin does not seem to be able to act on the intact brain when injected into the living animal. Would it be feasible to try to obtain enzymes, or enzyme extracts, from the tissues of patients with demyelinating disease and see whether the same picture could not be obtained with their use?

DR. JOSEPH M. FOLEY: Has Dr. Morrison stained a single, small piece? I understand that he has stained blocks. Is there any selectivity of various nerve tracts to these enzymes?

DR. HANNIBAL HAMLIN: Most of the breakdown products of demyelination are lipids—combined fats. Dr. Evelyn Man has described a method for determination of total lipids in the cerebrospinal fluid. It is a rather difficult quantitative technic, requiring large specimens of fluid. In the few cases of demyelinating disease that were sampled an increase in total lipids was shown. Although not elucidating the pathologic process, this method of study should be of diagnostic value.

DR. MADELAINE R. BROWN: This paper opens a great new field for neurology. What impresses me as I think back were cross sections of the spinal cord stained with Weigert's stain in cases of pernicious anemia and of multiple sclerosis. These are two diseases characterized by demyelination; yet the sections of the cord are entirely different. In pernicious anemia there are only holes. What is the chemistry of the myelin breakdown in multiple sclerosis that stimulates glial overgrowth? It is only through such work as this of Dr. Morrison's and Dr. Zamecnik's that the chemistry of these various processes will become known.

DR. PAUL C. ZAMECNIK: One can look on this type of experiment as a model. The enzymes were chosen not because it was thought that they exist in human or in animal brain but, rather, because they point to mechanisms by which myelin can be broken down. As Dr. Folch suggested, it would be interesting to get brains of patients with demyelinating disease and look for lecithinases or phosphatases that might contribute to the breakdown of phosphatides. Schoenheimer formulated the concept that in all living tissues, such as liver and brain, there is a constant turnover of their constituents. By analogy, the brain might be thought of as a house in which boards are continually being removed and new ones being put on, nails falling out and new ones being hammered in. Demyelination may result when the synthetic, or replacement, processes suffer, as well as when the degenerative processes increase.

DR. L. RAYMOND MORRISON: The sections in which the test and the control sections were on the same lantern slide were both cut about 20 microns thick.

The staining is a tough problem. We do not know why the myelin should not stain when lecithin is broken down. If the protein is broken down, will the myelin refuse to stain? If it does not, then we will not have that tool to work with. No one knows the details of staining the myelin sheath with hematoxylin.

Lower Nephron Nephrosis Following Electric Convulsion Therapy: Report of Two Fatalities. DR. LOUIS GOODMAN.

Two cases of lower nephron nephrosis following electric convulsion therapy were reported, with clinicopathologic evidence indicating that the electric current is capable of setting into motion factors leading to the development of progressive renal insufficiency. Evidence was presented showing that electric convulsion therapy produces temporary changes in the kidneys, resulting in urinary abnormalities in the majority of patients. This is in conformity with experimental evidence that electrical stimulation of area 13 (orbital gyrus) brings about renal vasoconstriction with shunting of cortical circulation to the medulla of the kidney.

The role of infection existing prior to electric convulsion thereapy as a factor in the pathogenesis of the syndrome was discussed. The relation of electric convulsion therapy to renal failure may be unsuspected because of the interval often lapsing between the onset of symptoms and the administration of the shock therapy.

The number of shock treatments received has no bearing on the development of renal complications. One patient received fifteen treatments; the second patient received only one. No explanation is available to account for this phenomenon; the existence of a crucial unknown factor, possibly infection, may be the essential component of a group of factors set into operation by the electrical stimulation of certain areas of the brain.

Attention was called to a possible danger signal of diarrhea following electric convulsion therapy. This occurs before laboratory evidence of renal failure and does not occur normally as a sequel to shock therapy.

The hypothetic possibility that therapy with the sulfonamides or streptomycin intensifies the renal lesions after electric convulsion therapy was pointed out.

Diffuse cerebral astrogliosis in both cases was attributed to factors other than the electric current, possibly to some toxic agent liberated in the kidneys.

DISCUSSION

DR. CLEMENS E. BENDA: I was critical at first because I was not convinced that Dr. Goodman's clinical evidence was conclusive, but the longer I listened the more I felt that he has made some very important observations. It is, of course, possible that the patient had severe encephalitis before shock therapy was started, but this is not likely, for the patient had no clinical symptoms of this type.

Any pathologist who has worked in a psychiatric hospital will agree that renal diseases are common among patients with mental disease and that it is frequently difficult to demonstrate such a condition by clinical tests. Dr. Goodman's pictures show that the condition of the kidneys was not that of a chronic disease, but that of a particular and rather acute disease. The paper was extremely stimulating, and we may watch more carefully for the relation between brain and kidney. With many defects of the brain one sees underdevelopment of the kidneys or cystic degeneration, and newer observations indicate a close relation between certain brain centers and capillary regulation in the kidney.

DR. HALE POWERS: Fatal lower nephron nephrosis, due to myoglobin, is known to occur in horses when they are suddenly required to make great muscular exertion, not preceded by a period of lighter exercise to condition the muscles and the circulatory system for this work. It seems to me that this is exactly what occurs in shock therapy. In a patient who has been for some time inactive, all the muscles suddenly begin to contract, more violently than they ever do in voluntary motion. Dr. Tracy Mallory studied lower nephron nephrosis in men in combat, and he told me that he found the condition only in those who were wounded or in a state of shock. However, its occurrence in man after convulsion therapy is so similar to what occurs in horses that I think that one should consider the wisdom of preparing patients before subjecting them to convulsion therapy. If a period of light exercise, preceding great exertion, will prevent the occurrence of lower nephron nephrosis in the horse, perhaps the same procedure will prevent its occurrence in man when subjected to convulsion therapy.

DR. WILFRED BLOOMBERG: At the Cushing Veterans Administration Hospital in the past year we have had 5 or 6 cases of lower nephron nephrosis, and all but 1 of the patients died. In the earliest case or so, we searched frantically for a source of carbon tetrachloride, or some other toxin, but none was ever found. The time relation between onset of illness and death was about the same as that reported here, and the pathologic picture, as well as the laboratory findings, was identical.

This has been an interesting paper, but I wonder if it is possible to tie this condition to electric shock therapy as an etiologic agent. It seems to me that with lower nephron nephrosis increasing in incidence, and with the tremendously wide application of electric convulsion therapy, it is more than likely that the coexistence of the two conditions may be merely coincidental. It is interesting to try to link the two together, but one should maintain a marked skepticism and should not be too quick to accept a causal relation between the two.

DR. MADELAINE R. BROWN: I wondered about the infection of the skin. The patient apparently had pustular folliculitis, which might have contributed at the time.

DR. LOUIS GOODMAN: I welcome this skepticism. I am not entirely convinced myself. I wished, however, to call to your attention the possibility that lower nephron nephrosis may occur as a complication of electric convulsion therapy. Only if we are aware of this complication will it be possible to establish a causal relation in future cases. There are crucial gaps in the histories of both cases which obliges me to leave some questions unanswered.

I am very much obliged to Dr. Benda and the other discussants for their favorable, as well as their critical, comments. With regard to the incidence of renal disease in psychiatric hospitals, I want to point out that it is mostly in the elderly group of patients that one finds renal disease and this is most commonly of a degenerative nature. In fact, surprisingly few cases of acute or chronic inflammatory diseases of the kidneys come to my attention at the autopsy table. Our 2 patients were middle-aged and showed no evidence of antecedent renal disease.

Dr. Powers suggested that the patient indulge in exercise before the administration of electric convulsion therapy. Unless the electric shock causes muscle injury, with breaking down and liberation of myoglobin into the blood stream, I do not see how such a procedure would help. One cannot tell which patient will have renal complications. Thousands of patients have received electric convulsion therapy without suffering any ill effects. There must be some factor, as yet undiscovered, which is set into operation, in the rare case, by the electric current which opens the way for the development of the renal syndrome.

Dr. Bloomberg's observations are of interest to me because I thought of the possibility of carbon tetrachloride poisoning in the second case, but the history did not reveal such a factor. Furthermore, one would expect symptoms to have developed sooner than after two weeks if the patient had taken the poison. Pathologically there was no further evidence of carbon tetrachloride poisoning, there being no focal necrosis of the liver.

Dr. Brown's comments on the cutaneous lesions are pertinent. We all thought that they were related to the clinical picture. All blood cultures, however, proved to be sterile. Our consultant, Dr. Ronchese, one of the prominent dermatologists in this region, was definite in his opinion that the lesions reflected a local condition of the skin and were not related to the systemic symptoms.

Pain Threshold Apparatus. DR. CLARENCE J. CAMPBELL.

This apparatus was constructed to make available for students and for clinical use a simple machine which could serve to determine the "pain threshold" or be used as a thermal probe in mapping sensory areas. It consists of a single short (1 cm. or less) resistance wire shaped as a letter S and mounted for convenience on the end of the hard rubber hand piece of the usual student Harvard electrode. The current flowing through this small S-shaped wire (and the temperature of the wire) is controlled by placing a variable resistance in series with the wire and the source of electrical energy. The duration of the current flow is controlled by a switch driven by a synchronous motor so arranged as to close the circuit for three seconds every fifteen seconds when the apparatus is used for "pain threshold" determinations. The current flowing through the hot wire may be read on an ammeter placed in the circuit or estimated by placing a voltmeter across the terminals of the probe. To use as a thermal probe, the motor-driven switch is stopped in the on position and the temperature of the wire set by adjusting the series resistor. The use of the thermal probe calls for no further comment.

Pain thresholds are measured by adjusting the temperature of the wire which is applied to the skin of the dermatome in which one is interested. The subject

is instructed to say "Now" when he experiences "pricking pain." "Pricking pain" is considered to be that component with no affective value except perhaps mild surprise. Noxious stimuli, such as those sufficient to produce withdrawal, are not used. Pain may be elicited without any preliminary sensation of heat. The end point or threshold is considered to be the current value shown when the subject's "Now" coincides with the drop of the indicating meter to zero. Since, to satisfy the clinician, the wire is heated every fifteen seconds, a new spot on the skin is chosen for each application. This facilitates cooling of the wire and prevents summation of thermal stimuli at any one point.

With a well instructed and normal, healthy subject, and with the average readings of a half-dozen or more applications used as the threshold, the pain threshold is quite uniform. A detectable elevation of threshold follows the exhibition of 0.6 Gm. or more of acetylsalicylic acid. Depression of threshold has been noted to follow ischemia. In our climate on cold days the threshold as measured on the hands is transiently elevated immediately after coming indoors. This is most pronounced if the skin is dry. Experiments in which the duration of the heating is varied give an intensity-duration curve resembling the usual chronaxia curve. From the information yielded by this curve, it seems that greater accuracy might be obtained by using a duration of the order of one second, rather than as three seconds.

For the apparatus to be a proper one, it should be calibrated so that the stimulus may be readable in terms of standard units of energy. At present ammeter (or voltmeter) readings are simply noted. The importance of multiple tests to determine threshold may be illustrated by the following tabulation taken on the same subject in one test.

The average threshold for the same subject with cold, dry hands was 0.300.

	No Sensation Evoked		Heat Only		"Pricking Pain"	
Ammeter Reading	No.	%	No.	%	No.	%
0.230	29	24.3	70	58.8	20	16.8
0.240	4	5.97	45	67.2	18	26.8
0.250	3	5.45	14	25.4	38	69
0.260	0	0	2	9	20	91
0.270	0	0	1	8	11	92
0.280	0	0	0	0	5	100

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY AND THE MASSACHUSETTS SOCIETY FOR RESEARCH IN PYSCHIATRY

David Rothschild, M.D., *Presiding*

Joint Meeting Jan. 15, 1948

Clinical Indications for Prefrontal Lobotomy. DR. ROBERT E. ARNOT.

Who should have a lobotomy? How can the psychiatrist tell which of his patients will benefit by the operation? These are the questions that this study is designed to help answer. Certainly lobotomy should not be done until other therapies which have a reasonable chance of success have been tried. But I am out of sympathy with the theory that lobotomy should be done only after everything else has failed, or, worse still, because there is nothing else to do. There

must be positive indications for lobotomy, indications such that in a given case lobotomy becomes the treatment of choice. It is these positive indications that my associates and I are trying to find.

Our material includes over 390 cases in which the operation was performed at the Boston Psychopathic Hospital, through the cooperation of the Lahey Clinic. My own experience includes interviews with more than 285 patients on whom lobotomy was performed.

Because the Massachusetts Society for Research in Psychiatry likes to have papers presented on work that is still in progress, we are willing tentatively to separate for consideration from our clinical material a group that presents as a clinical picture a fixed state of tortured self concern.

The patients with this clinical picture show intense worry, fear and depression. Some of them show marked paranoid ideas with persistent ideas of reference. Their thoughts go around and around on the same subject. As soon as the physician asks, "What is your chief complaint?" he is besieged with statements to the effect "I am depressed," "I am being persecuted," "I am afraid," or "I have pain."

Where are cases with this clinical picture to be found? Under which of the present hospital discharge diagnoses do they appear? We have been able to separate out groups of cases with this fixed state of tortured self concern from five diagnostic categories.

The first group of cases was found under the heading of manic-depressive psychosis, depressed phase. In some of the cases the diagnosis was involutional melancholia or agitated depression. These patients show intense self concern with worry, fear and depression. A sample case is that of B. L., a married woman aged 70, who said, when interviewed, "It's been the longest day and night I ever knew. I want to be with people, but I can't stand it." She appeared miserable and could not sit still. She had been sick for three years. A short course of electric shock therapy had not helped. She is greatly improved since lobotomy.

The second group of cases is found under the heading of paranoid condition. The patients who are helped are those with florid ideas of reference with real fear and worry. There is generally no fixed delusional system or chronic auditory hallucinations. The paranoid complaint often is that something is happening to their bodies. Such a case is that of M. L., a woman aged 56, who had owned and successfully operated several delicatessen stores. Her chief complaint was, "They've been using the stuff on me." She went on to relate how for the past nine years people about her had been sprinkling into the air a powder that aroused sexual feelings in her. She had had no previous treatment. Since operation she is much improved.

The third group of cases is found under the diagnostic label of schizophrenia. These cases are characterized by fear and by worry about their ideas of reference. They may have been sick for several years but have never had chronic auditory hallucinations. Some show marked perplexity; some, strong negativism. Such a case is that of M. L., a woman aged 22, who showed intense self concern with real bewilderment about her many ideas of reference. She was not hallucinated. She had had a gradual development of her illness over nine years and had shown no more than temporary improvement from prolonged insulin and electric shock treatment. This patient is now working as a salesgirl and has made an excellent improvement after the operation.

A fourth group of cases is found in the category of psychoneurosis, obsessive-compulsive type. The patients show persistent worry, fear and often mild depression. They plague the psychiatrist with their complaints. Such a case is that

of G. T., a woman aged 45, who had the phobia that she might catch a venereal disease. She had washed her hands and been fearful for much of the twenty years of her married life. Metrazol shock treatment had produced good improvement of several years' duration. Electric shock had been less helpful. After the lobotomy she showed marked improvement in regard to her symptoms, but, like several of our patients with an obsessive-compulsive psychosis, she presented a difficult management problem in the postoperative period because of her quarrelsomeness.

A fifth, and final, group of cases is that of patients with chronic pain. Certain of these patients show intense self concern with worry and some depression. They are almost constantly preoccupied with thoughts about their pain. Such a case is that of E. M., a widow aged 66, who made the chief complaint, "The whole right side of my face is paining and burning." She showed definite agitation and depression. This pain had been with her for one and one-half years and had not yielded to injections of alcohol or to posterior root avulsion. Since the operation she has not complained of the pain. She has also made a very good personal adjustment.

Summary.—We selected from among our patients undergoing lobotomy a group with a fixed state of tortured self concern. These patients show worry, fear, depression and sometimes paranoid ideas. We have indicated that cases with this clinical picture may be found under five of the present diagnostic categories: manic-depressive psychosis; paranoid condition; schizophrenia; psychoneurosis, obsessive-compulsive type, and chronic pain. It is our opinion that when this clinical picture becomes fixed and persistent, one has a positive indication for prefrontal lobotomy.

The Electroencephalogram Before and After Lobotomy. DR. MILTON GREENBLATT.

A total of 209 electroencephalographic studies were made on 70 patients who underwent lobotomy. Of these, 50 patients were clinically free from convulsive seizures; 19 patients had convulsive seizures in the postoperative period, and 1 patient was known to be epileptic before operation. Both prelobotomy and postlobotomy electroencephalographic studies were made on 50 nonepileptic patients, and on 11 epileptic patients. Serial postlobotomy electroencephalograms and follow-up records were made for a large part of the total group.

Immediately after lobotomy, the patient characteristically goes into a peculiar drowsy-akinetic state, from which he is readily, but only temporarily, aroused by stimuli. This condition lasts usually four to seven days, but may extend over weeks. The electroencephalogram characteristically shows diffuse irregular slow activity, some marked in the anterior aspect of the hemispheres. Arousal by stimuli, physical or chemical, results in a reduction of slow waves. There is a strong tendency toward reversal of the electroencephalographic picture to the normal pattern within a few months, paralleling the patient's clinical recovery from the operation.

Some patients continue to show abnormalities late in the postoperative period (six months or more after operation). These abnormalities are usually rolling, slow waves in the frontal, precentral and temporal leads, paroxysmal effects, focal exaggerations of slow activity in one hemisphere and increased response to overventilation. For the patients who have postoperative convulsive seizures, these abnormalities are marked, and focal dysrhythmias in particular are striking. There was more dysrhythmia in the prelobotomy electroencephalograms of the patients who had postoperative convulsive seizures than in the records of those who did not.

The initial postlobotomy electroencephalographic pattern is thought to reflect two factors primarily: cerebral trauma and a secondary drowsy-akinetic state. Late postoperative electroencephalographic abnormalities may presage clinical complications, including convulsive disorders. Although bifrontal dysrhythmia and focal dysrhythmia are more pronounced in patients with seizures, it should be emphasized that these abnormalities may also occur in patients with no seizures, neurologic changes or clinical complaints.

Stimulation of Orbital Surface of the Brain During Lobotomy. Dr. William P. Chapman and Dr. Robert B. Livingston.

DISCUSSION ON PAPERS BY DRS. ARNOT AND GREENBLATT

Dr. Walter Freeman, Washington, D. C.: The morbid self concern which so many of these patients show has been adequately dealt with, and yet I do not know that this should be the only criterion. There are a number of persons who show intense emotional response to their ideational activities, and one might say that they are projecting their ideas on the outside world and showing a tremendous hate. When it is recalled that unless one is afraid of a person one cannot hate him, it is clear that fear is the basis of hate. Without fear there can be no hate. A great many persons who are extremely active, vicious, hostile and hateful can be benefited by lobotomy. There are other, more unusual types of reaction that have been mentioned in the literature, such as chronic depersonalization, battle neurosis, sexual psychopathy and epilepsy, for which good results have been reported. The question of operation on criminals has been called to the fore in the last few months, and some reports have been made. Porteus and Peters, in Hawaii, report on 3 murderers. It would seem that the obsessive type of criminal might benefit from lobotomy.

As to the postoperative convulsions, the patients' families are upset by them. I do not know of anything more embarrassing than to have the family telephone after things have gone well and say that the patient is having a fit. We try to make light of it and tell them that we have patients who are not doing well in whom we actually induce convulsions. Watts and I went over the records of outpatients and found that most patients have convulsions within five years, if at all. About 7 per cent of patients with the one operation, 20 per cent of those with two operations, and about 40 per cent of those who had had a good deal of shock treatment and one operation have fits. The element of cerebral trauma is thus indicated. To encourage the surgeon, we can say that 7 of 10 patients who have had seizures return to normal. Not only do the patients fail to have further seizures, but their electroencephalograms tend to clear up fairly adequately. I do not think that the electroencephalogram is a very good guide to the development of seizures. We have had some patients who have been studied before and after lobotomy and before and after convulsions. We have come to the conclusion that abnormal waves are the effect of convulsions. They appear subsequent to convulsions and disappear as the convulsions stop. Some patients have persistent convulsions, and our efforts to control them have not met with complete response. Such cases still embarrass us.

Dr. David Rothschild: Dr. Freeman's observation that shock treatment tends to foster development of seizures is interesting. It makes one wonder what shock treatment may do to the brain.

Dr. Robert S. Schwab: I should like to comment on Dr. Greenblatt's paper, which is an important piece of work and in agreement with other papers on this

subject. It would be interesting if Dr. Greenblatt would correlate these electroencephalographic abnormalities with the results of neuropathologic studies to find out the nature of the lesions that made slow waves persist. Similar abnormalities appear in the postoperative records of patients examined the first week after removal of a cerebral tumor. The abnormal activity is usually localized to the area of operation. Since the operation is on the anterior part of the brain and he reported on motor and frontal areas, I wonder whether he had made observations on the occipital lobes. These observations are important and I feel that his finding of greater abnormality in the electroencephalograms of patients who had an abnormal prelobotomy tracing may serve as a brake on too much enthusiasm in the surgical treatment of such patients.

DR. DAVID ROTHSCHILD: Lobotomy has provided excellent opportunities for neurophysiologic and psychologic investigations. What does it do to the patient? From our experience in Worcester, which is limited, as compared with the experience of Dr. Arnot, I do not feel that one can choose one particular syndrome and predict with any great certainty that the results will always be good. My colleagues and I have seen surprisingly good results in very chronic cases. I should say that some of the best results, considering what we began with, were in our most chronic cases.

DR. ROBERT E. ARNOT: For discussion in the five minutes at my disposal I have selected a group of cases in which there was the chance of a good result.

DR. JACOB E. FINESINGER: What is the prognosis in hypochondriasis?

DR. ROBERT E. ARNOT: Some of our patients have had a history of hypochondriasis leading to psychosis.

DR. IVES HENDRICK: How about patients with chronic mildly paranoid states?

DR. ROBERT E. ARNOT: Paranoid patients would have to show a good deal of intensity in ideas of persecution. Their condition is more like agitated depression with paranoid trends.

Effects of Myanesin® in Rabbits Undergoing Electric Shock. DR. WILLIAM L. HOLT JR., DR. MAX RINKEL, DR. MILTON GREENBLATT and DR. RICHARD ANDERSON.

A safer drug for modification of convulsive rigor in electric convulsion therapy is needed, as fatalities occur because the muscle-paralyzing drugs now employed must be given in nearly lethal doses in order to be effective. Berger and Bradley (*Lancet* **252**:96 [Jan. 18] 1947) described the physical and pharmacologic properties of α-β-dihydroxy-γ(2-methylphenoxy)-propane, called it myanesin® and stated that its muscle-paralyzing effect made it worth a trial for the prevention of traumatic complications in electric shock convulsions.

We tested the effect of myanesin® in rabbits given electric shock in a manner simulating that of electric convulsion therapy for human subjects. Rapid administration of 100 mg. of myanesin® per kilogram of body weight was followed by death with respiratory paralysis. Slower administration of 75 mg. of myanesin® per kilogram produced paralysis of the muscles of the trunk and limb and unresponsiveness to the electric shocks used. Limb movements appeared seven minutes after injection of 75 mg. and three minutes after injection of 50 mg. Smaller doses did not regularly produce paralysis. As little as 10 mg. per kilogram of body weight raised the convulsion threshold 100 per cent, and the resulting convulsion had no tonic phase even if the current was increased fourfold. Though 10 mg. produced no discernible paralysis, its modifying effect on the convulsive

pattern was evident for twenty minutes. The fit was ushered in by a jump and after an inactive phase, terminated in running movements unless three fourths of a lethal dose of myanesin® was given and the current stimulation administered within two minutes. Thrombosis of the veins produced by injections was a troublesome complication, attributed to the propylene glycol solvent.

Work on human subjects with myanesin® should await the development of potent, but less irritant, solutions. Myanesin® is promising for the prevention of those complications which are caused by the tonic phase of the convulsion.

Changes in the Autonomic Nervous System Following Electric Shock Therapy in Psychoneurotic Patients. DR. DANIEL H. FUNKENSTEIN and DR. MILTON GREENBLATT.

For the past two years we have been using as a test of function of the autonomic nervous system in mentally ill patients the psychologic and physiologic responses to sympathetic stimulation (intravenous injection of epinephrine hydrochloride) and parasympathetic stimulation (intramuscular injections of methacholine). Briefly, the method consists in giving measured doses of these drugs and in following the systolic blood pressure for a certain period. Whether or not anxiety is precipitated is noted, and the resulting data obtained are correlated with the clinical picture. From these data we have constructed graphs with the blood pressure as the ordinate and the time as the abscissa in order better to visualize the data.

As a result of this test we have been able to classify cases of psychoneurosis, anxiety type, into four groups, each of which has fairly characteristic blood pressure patterns: (1) cases in which anxiety is precipitated by epinephrine alone; (2) cases in which anxiety is precipitated by methacholine alone; (3) cases in which anxiety is precipitated by either drug, and (4) cases in which the anxiety may be of any type, but a "chill" occurs ten to twenty-five minutes after the giving of methacholine.

The cases of obsessive-compulsive neurosis fall into two groups: (1) cases in which no anxiety is precipitated by either drug and in which there is a large sympathetic response in terms of the blood pressure response, and (2) cases similar to some of the anxiety neurosis type in that the anxiety is precipitated by methacholine. In some of these cases, in addition, "chill" occurs after the giving of methacholine, and in a few anxiety is precipitated also by epinephrine.

Effect of Electric Shock Therapy.—One of the effects of electric shock therapy is to increase the reaction to epinephrine and to decrease the reaction to methacholine. The effects on the various groups are as follows:

1. In cases in which anxiety is precipitated by epinephrine alone, after electric shock treatment there is an increased blood pressure response to epinephrine with a concomitant increase in the precipitated anxiety. There is a decrease in the reaction to methacholine. Clinically the patient is worse, as the anxiety attacks become more frequent and severer.

2. In cases in which anxiety is precipitated by methacholine alone, after electric shock treatment there is prompt clinical improvement concomitant with an increased reaction to epinephrine and a decreased reaction to methacholine, with the latter drug no longer precipitating anxiety.

3. In cases in which anxiety is precipitated by either drug, after electric shock treatment there are an increase in epinephrine-precipitated anxiety and absence of precipitable anxiety when methacholine is given. In terms of the blood pressure

responses, there is an increased reaction to epinephrine and a decreased reaction to methacholine. Clinically the patient is improved but still experiences anxiety attacks.

4. In cases in which a "chill" occurs after methacholine, the response to electric shock treatment is rapid, with the same changes in blood pressure found in the previous categories.

In the cases of obsessive-compulsive neurosis, the effect obtained after electric shock treatment depends on the type of case.

1. In the group in which no anxiety is precipitated by either drug and in which the responses are far over on the sympathetic side in terms of the blood pressure, there is no change clinically or in the autonomic responses after electric shock treatment.

2. In the group in which anxiety attacks typical for the patient are precipitated by methacholine there is clinical improvement after electric shock treatment, with an increase in the reaction to epinephrine and a decrease in the reaction to methacholine. These cases bear a certain resemblance to the cases of manic-depressive psychoses, but time does not permit a discussion of this aspect.

It should be emphasized that the same psychologic and physiologic changes seen after electric shock treatment occur when the patient's responses change spontaneously or as a result of other types of treatment; that is, the changes are not specific for electric shock treatment. The psychologic and physiologic changes are "part and parcel" of the same phenomena, and as one changes, the other changes concomitantly. They seem to fit like a "hand in a glove." Other changes in terms of this test follow electric shock treatment, but time does not permit their discussion.

DISCUSSION ON PAPERS BY DR. HOLT AND ASSOCIATES AND DRS. FUNKENSTEIN AND GREENBLATT

Dr. Mark D. Altschule: A subtitle to the paper given by Dr. Holt and his colleagues should be: "What is Wrong with Curare?" If there were no dissatisfaction with curare, there would be no impetus to look for other drugs. I do not think one can draw any conclusions about the clinical usefulness of myanesin.® Dr. Holt pointed out that additional studies should be made first. In the work on rabbits, there had to be an increase in the amount of current given in order to produce convulsions. It has been suggested that large amounts of current may be damaging to the brain, a phenomenon that might, however, be helpful. A great deal of work must be done before the question can be answered. In view of my complete inexperience with myanesin® I should like to talk about curare. When curare works well, it works beautifully. The patient has a convulsion with much less muscular contraction, and without a broken back. There are hazards associated with it. My colleagues and I seem to have had more than our share of untoward reactions. These have been so numerous in our experience as to result in our classifying them as to their nature and what to do about each type. We had one death about a year and a half ago; we have had none since. The reactions have been described in the psychiatric and in the physiologic literature.

1. Paralysis of the diaphragm. There may be a marked depression of respiration, together with striking depression of all other muscular activity. We have never seen it, probably because we have never used doses large enough. What we have seen is a paralysis of respiration without paralysis of the rest of the body. That is most disturbing because it is not discussed in the psychiatric literature.

2. Central respiratory paralysis. With this we had had most trouble. This effect is known to physiologists. It has been established that electric shock depresses respiration. When, in addition, respiratory depression is increased by curare, the patient may die. Central respiratory depression is likely to be confusing because during the course of electric shock carbon dioxide accumulated in the body acts as an excellent respiratory stimulant. The patient blows that off, and he no longer has a respiratory stimulant. He is put into a side room alone and may then die. We have seen 7 patients who showed this reaction, but it was detected in time and treated appropriately. These patients were able to move all their extremities but were unable to breathe at all. They had a type of respiratory depression which is limited to respiratory muscles, and is probably central. We put a tracheal tube into the nose and blow oxygen into it and have no trouble.

3. Impurities in the solution of curare used. We have used more recently a solution of crystalline D-tubocurarine which has caused no difficulty. The original solution contained unknown tertiary amines (which inhibit cholinesterase). The vagus nerve is stimulated during the convulsion. Vagal stimulation slows the heart and causes narrowing of the bronchi. If during strong stimulation of the vagus something which inhibits cholinesterase is introduced, heart block may occur. The electrocardiogram showed periods of heart block in our patients so treated. The solution used several years ago inhibited cholinesterase and thereby exaggerated the phenomenon of electric shock. Now these tertiary amines are no longer present. They were largely what was wrong with curare. It is possible that in myanesin® some, or all, of these defects will be avoided. At present, central respiratory paralysis is the only thing that bothers us, and we can manage that by watching the patient and starting administration of oxygen by tracheal catheter promptly.

I was confused by the second paper. In the field of the physiology of mental disease, or the physiology of electric shock, there is no framework of reference, such as exists in diseases of the kidney, or of the heart, to serve as a basis for understanding and comparison. It is difficult for me to evaluate the role and significance of Dr. Funkenstein's work in regard to the problem of anxiety and the problems of electric shock. That may be a reflection on me rather than on Dr. Funkenstein. There might be criticism in regard to the technics he used. Studies have shown that epinephrine is sometimes oxidized. When one injects epinephrine, one may not be measuring the effect of epinephrine; one may be measuring potency of a substance which destroyed it or the rate of excretion. In most physiologic work, instead of using a single injection, it has come to be the custom to inject dilute solutions at a constant rate to secure a constant effect. Many physiologists would object to injection of a single dose intravenously and would object to intramuscular injections of a vagal stimulant. In addition, it is well known that when epinephrine is given there is an outpouring of acetylcholine. When acetylcholine is given, there is an outpouring of epinephrine; when one gives this drug in a single dose, one has no idea of what is going on. The fact that administration of these drugs is modified by electric shock merely adds to my puzzlement, and does not clarify the situation. Actually, the studies of Dr. Funkenstein do not measure changes in the autonomic nervous system but only indicate differences in responses to two drugs taken out of a bottle.

DR. ROBERT SCHWAB: A word about myanesin®. C. R. Stephen and J. Chandy (Clinical and Experimental Studies with Myanesin. *Canad. M. A. J.* **57**:463-468 [Nov.] 1947) found it very toxic. In talking with them in Montreal, I learned

that they have given it up and are looking further into curare. In addition to local thrombophlebitis at the site of injection, they reported hematuria of some severity and stated that in their opinion myanesin® is a dangerous drug.

DR. JACOB E. FINESINGER: Some years ago Dr. Lindemann and I found that we could differentiate four groups of patients with anxiety neurosis on the basis of their responses to injections of epinephrine and methacholine. One group reported that epinephrine reactivated the symptoms and the feeling of anxiety. Another group reported that their symptoms occurred after methacholine. A third group reported that the reaction took several days to develop, whereas a smaller group did not react to either drug. We also found that after epinephrine the patients became more introspective and more concerned with their internal processes, whereas after methacholine they were more concerned with external objects. I am interested to know whether Dr. Funkenstein found the same thing that we did. In 2 patients who recovered, one cured by a faith healer, we repeated the injections. In these patients we did not get the same subjective response as when they were sick. This makes us wonder whether patients are not in a different physiologic state when they are sick. We have wondered whether a state of localized cortical inhibition is set up when the patient is confronted with a pathogenic stimulus. As a result of this state of cortical inhibition, lower autonomic centers are released, with autonomic instability. In a similar fashion, certain types of ideas and feelings are released. We wonder whether changes in the cortical excitation or inhibition are not occurring during psychotherapy. It may be that certain types of doctor-patient relationship bring about physiologic changes of a similar kind, which might explain the patient's overreaction in the therapeutic situation.

As to Dr. Altschule's discussion, we are aware that injection of epinephrine into a patient starts off a complex process. This study is a good beginning. I want to congratulate Dr. Funkenstein on an excellent piece of work.

DR. DANIEL H. FUNKENSTEIN: In answer to Dr. Finesinger's comment on patients with anxiety neuroses in whom neither epinephrine or methacholine precipitated anxiety, I am sorry that I did not make myself clear, since we, too, had a few such patients. However, if one gives these patients electric shock treatment, their clinical anxiety attacks become severer, and then if one gives them epinephrine the anxiety is precipitated. These patients show, in addition to the anxiety precipitated by epinephrine, an increase in their blood vessel response to epinephrine and a decrease in that to methacholine as compared with those before shock. This would seem to be a case in which electric shock treatment is definitely harmful.

In the work done by Dr. Finesinger and Dr. Lindemann several years ago, they studied the psychologic responses but did not follow the blood pressure. We have corroborated their findings. An interesting correlation between their work and ours is that the psychologic responses of their patients changed nine to eleven minutes after the giving of methacholine. These psychologic responses changed from those that one would expect after methacholine to those that one would expect after epinephrine. That is identical with our findings when we used the blood pressure as the measure of the physiologic changes. At the end of nine to eleven minutes after giving the methacholine, we found that the blood pressure rose above the preinjection level, an effect which we interpreted as due to activity of the sympathetic nervous system. Thus, similar responses in this type of patient were observed by investigators using psychologic means and by other investigators using physiologic methods.

As to "palpitation," it is a fact that while physiologic changes in the heart occurring after epinephrine and after methacholine in almost all these patients seem similar, some patients will interpret as anxiety only the reaction after epinephrine; some patients, only the reaction after methacholine, and some patients the reaction to either drug. Some patients will not interpret the reaction to either drug as anxiety. In the light of present knowledge, this seems to depend on the psychologic interpretation of the peripheral autonomic phenomena by the individual patient.

In regard to Dr. Altschule's remarks, I am well aware that we do not understand the many mechanisms set in action by these drugs. We are presenting the observations we made, but we cannot offer an explanation of the mechanisms, as this would be mere speculation.

DR. WILLIAM L. HOLT JR.: The Canadian workers may have run into difficulties with myanesin® because of the solvent, rather than the drug itself. When we used a less irritating solvent, thromboses did not occur. I still hope that myanesin® in a nonirritating solvent may yet prove of some value.

Tapping Rhythms in Neuropsychiatric Patients. DR. PAUL G. MYERSON and DR. DAVID LANDAU.

Forty-five patients with various psychiatric conditions and 25 control subjects were instructed to tap at a comfortable rate. Studies were made on the influence of a distracting metronome beating both slower and faster than the comfortable rate. The capacity of the patient to shift to new rates was also studied. The influence of electric shock and lobotomy was studied in a number of patients.

A large group of the patients showed a much lower comfortable rate than the controls. Many were incapable of shifting to a new, fast rate. Electric shock treatment and lobotomy were associated with improvement in this capacity. Only 1 patient, who was schizophrenic, followed the metronome. A patient with Korsakoff's syndrome was markedly influenced by the metronome beating at about half the rate, with both faster and slower distracting stimuli.

Pervitin® in Neuropsychiatry: Comparison with Sodium Amytal and Amphetamine Sulfate. DR. JULIUS LEVINE, DR. MAX RINKEL and DR. MILTON GREENBLATT.

Because of undesirable effects of sodium amytal,® namely, intoxication, narcosis and amnesia, the authors were led to study pervitin® (D-desoxyephedrine), a drug similar to amphetamine (diamphetamine sulfate), which has a stimulating, rather than a depressing, effect on the central nervous system. Studies in the literature indicated that pervitin® had fewer untoward side reactions than amphetamine in equivalent doses. The authors studied the physiologic and psychologic effects of pervitin® (20 mg. intravenously) in 75 cases, comparing its action with that of sodium amytal® and amphetamine sulfate.

The physiologic effects of pervitin® were alteration of pulse, increased blood pressure, dryness of the mouth with thirst, loss of appetite, tightness in the chest, increased awareness of the environment and sensory stimuli, elimination of fatigue and wakefulness. No significant changes were noted in the electrocardiogram or the electroencephalogram.

The psychologic effects of pervitin® were a marked stimulation of emotionally charged material, which included painful memories, intimately personal fantasies and delusional ideas. The patient revealed new material and elaborated on old delusions. The psychologically rich response evoked by previtin® is helpful in

formulation of the individual case, both diagnostically and therapeutically. Amnesia was significantly absent for the material obtained. No subsequent untoward or toxic effect was observed.

Comparative studies were made with amobarbital sodium (250 to 500 mg.) and amphetamine sulfate (20 to 40 mg.) given intravenously. Thirty-five of the 75 patients were given sodium amytal® and 15 amphetamine.

The results indicated that pervitin® had advantages over sodium amytal® in that administration was less time consuming, the response was immediate and spontaneous, no slurring or thickening of speech occurred, the effect was appropriate for the material produced and there was no subsequent amnesia.

In our opinion, for the same milligram dose, pervitin® had advantages over amphetamine in that the psychologic material was usually richer and the affect more appropriate.

DISCUSSION

DR. SAMUEL WALDFOGEL: One of the interesting implications of Dr. Myerson's paper is that it presents further evidence that the speed of tapping, although apparently a simple neuromuscular response, is not unrelated to the subject's attitude toward himself and his own motor capacities. Thus it can be seen that speed of tapping fluctuates with motivation and change in attitude. The rigidity of the tapping rhythm noted in certain of the psychotic groups is interesting and is likely to be related to the strong perseveration tendencies found in these groups.

One factor that seemed to be neglected in the present study was the fluctuation of rhythm during a given period of tapping. When one asks a patient to tap at his maximum rate, one finds that this rate varies from one five second period to the next. The pattern of variation differs among different nosologic categories. Similar information on variation in "natural" tapping rate would be very desirable. Aside from this one minor deficiency, the study seemed to have been clearly formulated and well conducted.

DR. JACOB E. FINESINGER: I should like to ask Dr. Myerson about the motivation of these patients. Are the patients who follow the metronome more closely those who are more cooperative? In measuring talk, we found that one difference between the neurotic patient and the normal subject was that the normal subject could follow the stimulus. The neurotic patient had his own tempo and would go along in a stereotyped way, no matter what the examiner's tempo of talk. In contrast, the adjusted person would follow the changes in the physician's activity.

DR. PAUL G. MYERSON: We tried varying the stimulus situation. This was done sometimes by a charming young female assistant and sometimes by myself, and it seemed to make no difference. The level of aspiration does make a difference.

DR. DAVID ROTHSCHILD: May I ask about the use of this drug for intensive brief psychotherapy. Can it be used daily without ill effects, such as insomnia?

DR. JULIUS LEVINE: Because of insomnia and loss of appetite, subsequent injections of pervitin® were given two to three days apart. As a rule, it was not necessary to repeat the dose in so short a period, because the patient's improved mood remained for about a week. For example, an adolescent boy who blocked and was unable to overcome his own resistance became significantly productive under pervitin.® At the end of two weeks he began to revert to his original surly, sullen, defensive state. Pervitin® was administered, with resumption of a deeper relationship.

News and Comment

INSTITUTE OF NEUROSURGERY AND NEUROPATHOLOGY, SANTIAGO, CHILE

On Nov. 10, 1949 the Institute of Neurosurgery and Neuropathology of Santiago, Chile, completed ten years of work. This Institute has gained a special place in America, and for this reason many young physicians from South and Central America, as well as from Mexico, have come to specialize in these subjects.

The most important event in this celebration is the opening of two new departments: Neurological Surgery for Children and Rehabilitation for Paraplegics.

The Institute is directed by the well known neurosurgeon Prof. Dr. Alfonso Asenjo.

Book Reviews

A Textbook of Neuropathology with Clinical, Anatomical and Technical Supplements. By B. W. Lichtenstein. Price, $9.50. Pp. 474. W. B. Saunders Company, W. Washington Sq., Philadelphia 5, 1949.

This book deals with neuropathology in its many aspects and presents the science in a helpful and practical way. Problems are avoided as much as possible, and a great deal of controversial material, so often found in other books, has been omitted. Little theory is included in these pages and the newer technics have been slighted, but what the book lacks in profundity it compensates for in scope.

All the conventional categories of nervous disease have been fairly adequately covered: degeneration, inflammation, tumors and vascular disease; in addition, good chapters are included on muscle diseases, malformations and deformities. Then, too, there is a chapter on syndromes in which 114 diseases or symptom complexes are briefly described. In addition, a chapter on neuroanatomy and another on laboratory technic are included, but they are not likely to be of much assistance except to point the direction one must take to follow the discipline of neuropathology.

The work is profusely illustrated with photomicrographic reproductions, which, while often far from being works of art, are authentic and serve their purpose well. The book probably contains more detail than the medical student needs to know; on the other hand, it lacks the depth that a source book for the professional neuropathologist must contain. But for the beginner in neuropathology or the general pathologist interested in neuropathology, it is an excellent book, heartily recommended.

Atlas of Neuropathology. By William Blackwood, T. C. Doods and J. C. Sommerville. Price, $9. Pp. 200. Williams & Wilkins Co., Mount Royal and Guilford Aves., Baltimore 2, Md., 1949.

This atlas consists of a series of beautifully prepared illustrations in black and white and in color of normal and pathologic histology and the gross appearance of various lesions of the nervous system, both medical and surgical. The descriptions

are concise. There is almost no discussion or interpretation. The beauty of the illustrations and the simplicity of the presentations are adapted well to the instruction of students, but many pathologists and clinical neurologists also will find it useful. While the absence of haggling over minute details, so common in textbooks of neuropathology, is a great relief, the value of the text might be increased by more interpretation and reference to fundamental principles.

Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior. Second Edition. By Wendell Muncie, M.D. Price, $9. Pp. 620. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo., 1948.

This volume is a new edition, by the same author, of the text published in 1939. In the author's words, "This second edition has been extensively edited in the light of my recent years devoted largely to private practice, and will indicate what I have found useful as concepts and as practice."

The size of the book has been reduced by about 100 pages. The historical appendixes of the first edition have been omitted. Again, the text has been divided into three parts: Part I: Psychobiology, the Study of Normal Behavior; Part II: Abnormal Behavior; Part III: Treatment.

Part I is entirely devoted to a chapter on the historical and philosophic basis of psychobiology, together with a study of the student's personality, in which personality development is taken up in the minutest detail, mainly on the basis of the student's evaluation of himself.

Part II includes a short historical account of psychobiology, in which it is compared with kraepelinian and psychoanalytic psychiatry. There is a long, detailed and excellent chapter on the examination of the patient. The remaining chapters in this section deal with the nervous psychopathologic states, using the accepted vocabulary and terminology of meyerian psychiatry. These chapters are filled with detailed case histories.

Part III deals solely with treatment and is broken down into chapters on general bases of treatment, important therapeutic aids and treatment of the various psychopathologic states.

As a psychiatric textbook, the book is well recommended, particularly to medical students.

Duodenal Ulcer: A Sociopsychological Study of Naval Enlisted Personnel and Civilians. By Jurgen Ruesch, M.D., and others. Price, $4. Pp. 118. University of California Press, California Hall, Berkeley 4, Calif., 1948.

Ruesch, and essentially the same group of colleagues who presented a monograph entitled "Chronic Disease and Psychological Invalidism," have now produced a somewhat less detailed study of duodenal ulcer, with emphasis on sociologic and psychologic factors. The study lays special emphasis on situational difficulties and their relation to the character structure of the individual patient, with the hope that a knowledge of psychodynamic forces within these patients would aid in their rehabilitation.

In all, 20 volunteer civilians and 42 volunteer naval enlisted personnel who had a duodenal ulcer demonstrated roentgenologically were studied. This study covered periods of from three or four days to one week in the wards of the

Langley Porter Clinic, and eight to ten hours were spent in focused interviews and physical and roentgenographic examination. Areas for investigation included onset of symptoms, war experiences, attitudes toward authority, attitudes toward medical personnel, detailed childhood history and relationship to parents and siblings. The last area for investigation was the patient's present day personality.

Modifications of the Wechsler-Bellevue, Minnesota Multiphasic and Rorschach tests were used and the results compared with records previously obtained for their patients with delayed recovery.

This study again demonstrates the high rate of incidence of initiation or exacerbation of symptoms in patients with ulcer in relation to a stressful situation. These environmental difficulties are not stress situations in the usual sense, such as bombardment or combat, but, rather, are concerned with adjustment to new cultures, ways of living, change of status and separation from loved persons.

The observation that these persons have higher intellectual endowment and lower occupational achievement than patients without ulcer is not well defended. Formal testing elicited general trends indicating lack of flexibility in social technics, dependence and psychologic obtuseness.

The analysis of the patients' attitudes to parents is interesting. It was concluded that separation of the warm source of affection from the main source of authority was essential in normal childhood development. This pattern was absent in the patients studied, and the investigators also felt that these men regarded self assertion as synonymous with alienation of affection. Review of sibling relationships revealed factors which tended to isolate the patients who later had ulcer from the rest of the children.

Study of the adult characteristics of the men with duodenal ulcer revealed primary conflict over dependency, with secondary emphasis on the areas of aggression-nonaggression and masculinity-femininity conflict. In the overtly dependent group, there was attachment to a parent or a parent substitute, or oral gratification was sought through food, drugs and alcohol. The second group, in which were included the classic ulcer types, such as the driving, successful business man, seemed to behave in an independent fashion. On closer examination, it was felt that these men handled their basic dependency needs by counterreaction or overcompensation. The third group made violent rebellion against authority, and the fourth group were persons whose dependency conflicts were overshadowed by other problems. It was here stated that changes in environment which tended to separate these persons from their primary source of reassurance, or situations which made counterreaction or achievement impossible, precipitated a breakdown.

There is also a chapter on attitudes toward the physician; it does not appear surprising that there should exist such irrational attitudes. The most neurotic of the group in terms of personality profile sought most support from the physician.

The book is rounded out by several case histories and rather good charts, as well as by a brief, but satisfying, survey of the recent literature. The volume is recommended reading for persons interested in psychosocial and physiologic correlates.

Die Reaktion der Pupille auf Mydriatica nach Unterbrechung der sympathischen Pupillenbahn. By Peter Wormser. Price, 17 Swiss francs. Pp. 160. S. Karger, Holbeinstrasse 22, Basel, Switzerland; 215 4th Ave., New York 3, N. Y., 1948.

This work demonstrates in a drastic and frightening way how far specialization in medicine has gone. A monograph of 160 pages, including 16 pages of ref-

erences, is devoted exclusively to the subject of "Reaction of the Pupil to Mydriatics After Interruption of the Sympathetic Pupillary Tract"!! The presentation is compact, it is true, but it still reminds one of the words of Martial (40-102 A. D.), "What is the use of brevity if it constitutes a book?" The work is a thorough clinical, and particularly literary, study. It is based on 22 clinical observations and on 2 animal experiments. The problem is tackled from every angle—anatomic, pathologic, physiologic and pharmacologic. The author exhausts his subject—but not the reader, since the presentation is vivid, the work is well planned and the plan well executed and strictly adhered to throughout.

A Doctor Talks to Teen-Agers. By William S. Sadler, M.D. Price, $4. Pp. 366. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo., 1948.

This book is written for adolescents and apparently is intended as a sort of guide through the stormy "teen" years. There is no question that such a book is sorely needed and that it will be welcomed by adolescents and their parents alike. A series of topics, all of which are vitally important to adolescents, is treated. The author has attempted to give concrete answers to perplexing questions, including such vital issues as one's relationship to one's self, relationship to parents, other interpersonal relationships, vocations, sexual adjustments and religion.

Unfortunately, the language is glib and the text full of platitudes, which offer little real help to the bewildered adolescent. There is a strong moralistic overtone throughout. The author attempts to sugar-coat his advice with superficial case histories, told in storybook form—this in a book with topics and subtopics in the style of a textbook. Many subjects are only briefly mentioned, then dropped. The author's attitude is that, with courage and will power, all adolescents can change themselves and their environment so that everything will be happy in the end! However, it is only fair to say that in forty years of practice the author has found certain concepts to be useful and has honestly and sincerely offered them in an attempt to help adolescents and their parents.

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CONTENTS